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SURGICAL TRENDS SINCE THE TURN OF THE CENTURY*

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BOSTON

IT WAS with sincere pleasure, but with a keen sense of my own shortcomings, that I accepted the invitation to deliver the first annual Peer P. Johnson Lecture in Surgery, established as an expression of admiration and loyalty for your chief. I am happy to have the opportunity to show my appreciation of his friendship and my esteem for his qualities as a surgeon — feelings that have strengthened with the years. I believe, too, that I have a tenuous tie with the Beverly Hospital because my uncle, Edward L. Giddings, was on the first Board of Directors, when it was incorporated in 1893. This institution was the outgrowth of the small private hospital started with courage and wisdom by Dr. Samuel William Torrey five years earlier. Finding that the growing demands were more than he could meet, Dr. Torrey, with great magnanimity, gave his holdings outright to the corporation. It was not long, however, before the hospital again outgrew its quarters. The present lovely site was acquired, and in September, 1908, the main building of the present hospital opened its doors. The quality of care given the sick has steadily augmented the stream of patients, and year by year additions have been demanded until it stands today, a superb and beneficent haven of refuge for the sick.

The man in whose honor this lecture has been established has lived in a vivid and exciting time in the development of the medical and surgical care of the patient. He has watched the scene change from the inefficient haphazard care of the patient in his home to the present scientific treatment in a modern, fully equipped, smoothly running institution. He was one of the pioneers in this advance, and it was largely through his zeal and determined effort that this vital boon to the community developed so magnificently. He was blest from the start by a far-seeing, co-operative board of hospital managers, who have aided him in bringing his plans to fruition. Improvement and expansion of the surgical service have gone hand in hand with the development of the hospital. Familiarity with the latest advances in surgical management and evaluation of new technical procedures are necessary in the best interest of the patient and to provide the resident and intern staffs with the best in surgical instruction. This has meant constant study and many an hour spent burning the midnight oil. The sphere of his influence has traveled far beyond the hospital walls as his well trained residents have gone forth year by year to embark on their professional careers.

As he completes the half century of work in his chosen field, he can look back over the busy years, striving always for the goal that he raised ever higher and more difficult of attainment as time marched on. Few of us have had the great satisfaction that must be his in seeing his dream come true and few of us merit so deservedly the honor and esteem of his friends, co-workers and students. His life epitomizes my father's standard of the true surgeon. In his presidential address before the American Surgical Association in 1918, he said:

> Were it not for the unattainable the world would indeed be a poor place. Those qualities that make the true man in any walk of life, are doubly necessary to the making of the real surgeon.
>
> Self-reverence, self-knowledge, self-control,
> These three alone lead life to sovereign power,
> Yet not for power (power of herself
> Would come uncalled for) but to live by law
> Acting the law we live by without fear;
> And, because right is right, to follow right
> Were wisdom in the scorn of consequence.

Heartiest congratulations are due Dr. Johnson for his outstanding accomplishments as chief of staff of the Beverly Hospital and as a skilled and humanitarian surgeon.

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The tendency to reminisce is an indication of senility, but I am going to risk being placed in that category since I believe many of you do not realize the vast changes that have taken place in the practice of medicine in the last fifty years, since the horse-and-buggy days. Widely diverse factors have played important parts. Electricity, the telephone and the internal-combustion engine, which made possible the automobile with its demand for good

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roads, have influenced the course of this development as surely as improvement in medical education, abolition of the diploma mills and the establishment of scientific research departments in medical schools and hospitals.

Let us take a few moments and turn the pages back to the first decade of this century to see how the practice of a busy surgeon was carried out in those days. When my brother Jason and I had completed our internships at the Massachusetts General Hospital and came on as assistants to my father in 1907, we had no office nurse, and one of our duties was to keep in readiness two bags with a full kit of instruments, sutures and solutions and two other bags containing the dry goods, which we sterilized in an open steam sterilizer over a gas burner. Surgical emergencies were frequent, for there were no trained surgeons in the smaller communities, and in the absence of a local hospital, many operations had to be performed in the patient's home. When the physician in attendance called up he would usually say "I have a surgical abdomen here. Can you come out prepared to operate?" This would leave the diagnosis a bit nebulous, and one might find anything from an acute appendicitis to a perforated ulcer or strangulated hernia.

In summer it was a question of going by motor, and a big question it was, particularly at night. There were no through routes, only dirt roads, unreliable cars and acetylene headlights that always ran out of carbide. In winter the roads were unplowed, and one drove to the station for the early morning train at 5 or 6 o'clock with the two bags, picking up the assistant and a nurse on the way. In the sleigh from the depot to the patient's home a history could be obtained from the doctor. At the house each one had his work allotted. The surgeon took a more careful history and examined the patient. The assistant first stoked up the kitchen stove, got the water boiling and put in the instruments to sterilize and then went up to prepare the patient, after which he started to scrub at the kitchen sink with running water, if it existed; if not, the hand pump and a basin sufficed. The nurse in the meantime got out clean linen and made up the operating table with blankets for a pad. Generally, the best operating table was the dining table pulled apart and a couple of leaves laid lengthwise over the gap. This allowed the surgeon and assistant to stand sufficiently close to the patient for satisfactory operating, but the patient's physician, who acted as anesthetist, had a hard time. The nurse then had to lay the sterile tables for instruments and dry goods, and perform the other duties of the floating nurse. While the patient was being anesthetized she also took over the duty of orderly, which at times was strenuous in the stage of excitement during ether induction. I have always wondered why ether explosions were not of common occurrence, for operations were frequently done in the kitchen and by the light of kerosene lamps.

This type of surgery was unsatisfactory, since the surgeon was largely out of touch with his patient once the operation was completed. Nonetheless, it was surprising how good the results were, on the whole. I have a vivid recollection of assisting my father in a little farmhouse, where he operated on a woman with a huge ovarian tumor. With relaxation, under anesthesia, the patient had to be steadied on the table to prevent her being pulled off onto the floor by the weight of the cyst. The growth weighed 63 pounds, some 18 pounds of which was solid tumor. Today with plenty of blood for transfusion available and liberal use of fluid intravenously, we would expect such a patient to do well. Even then, with only subpectoral infusions and tap water by rectum for supportive therapy, the patient made a smooth recovery.

Subpectoral and subcutaneous infusions were practically discarded, for unnecessary pain was caused the patient. Of late, they have again been utilized with the addition of hyaluronidase to minimize undue discomfort during administration, particularly when repeated venepuncture has caused widespread thrombosis. The rectal method of replacing the fluid requirement should not be cast into the limbo of forgotten procedures, although I venture to guess that the intern and resident of today would rarely think of it. The rectum will retain up to a quart of water given slowly to the anesthetized patient, and the water will be absorbed in a physiologic manner instead of being forced down the throat, so to speak, by the intravenous needle, perhaps in excess of the demand.

Ingenuity was often demanded of the surgeon. With a hammer and a pair of tin shears, an internal angular splint could be readily constructed from an old tomato can. If an unexpected intestinal procedure was encountered and the intestinal clamps had been inadvertently left out of the kit, a couple of throat sticks and several rubber bands could be boiled quickly and would answer admirably.

None of the metropolitan hospitals in Boston had private wings, and patients from a distance were cared for in nursing homes converted from private dwellings. Patients in comfortable circumstances, living in Boston or its suburbs, preferred to be operated on at home. Community hospitals were springing up in the larger towns, where a large house had usually been purchased or donated and altered for the purpose. These provisions for private surgical patients would seem very primitive today. There were no interns or residents and no laboratories or diet kitchens. With an older nurse as superintendent and a corps of qualified graduate nurses, excellent care was given the patient, and it was a godsend to the busy surgeon to have many of his patients under one roof and not have to run all over town on postoperative visits.

If a determined lady, psychologically as well as financially independent, demanded that her hysterectomy be done at home, what would be the steps in the procedure? By then a surgical supply house would send a folding operating table and a trunk with all the necessary sterile dry goods, basins, sutures and so forth, to arrive at the house the day before. The assistant would pick out the best room available for an operating room adjacent to a bathroom and preferably with northern light. (It was the hardest thing in the world to prevent the neat New England housekeeper from giving the room a real spring cleaning and thereby setting the dust beneath the bureau and in the corners to swirling and eddying around the room to settle finally, the next day, on the sterile tables or perchance on the operative field.) The draperies were covered with sheets, and muslin had to be pinned across the windows or the windows soaped to prevent inquisitive neighbors from holding front seats. Next came the soap-and-water preparation and a soap poultice to be kept on overnight. The laxative was not forgotten. The old dictum had been "Bleed, sweat, purge and starve." Fortunately, "bleed" and "sweat" had been crossed off the list, but not purge and starve. The castor oil had been ladled out the night before, and by now the patient was thoroughly depleted and fairly successfully dehydrated, since she had been allowed little to eat and drink all day and supper would be tea and toast. In the light of today's knowledge it seems a wonder that patients survived operation after the ordeal of both preoperative and postoperative purgation and starvation.

With the advent of the community hospital, the treatment of the patient was vastly improved, and the work of the physician and surgeon in the care of the sick lightened. Life-saving facilities were at hand in the hospital that could not have been obtained in the home. Yet, strange as it may seem, a definite aversion to institutional care had to be overcome. Particularly among the more illiterate, there was a feeling that if a member of the family was taken to the hospital he would never come out alive. Fortunately, the life-saving service that was offered the community was soon recognized, and at the present time all such units have expanded and the original makeshift buildings have been largely done away with. Modern and complete hospital units of varying size designed by qualified hospital architects are replacing the old buildings. Provision is made for the ancillary services of the medical and surgical divisions: the laboratory, the x-ray room and the diet kitchen, with trained technicians for each. A well planned, smoothly functioning operating wing is a necessity, with trained personnel and an anesthesia department familiar with the methods of modern anesthesiology. It is a far cry from the farmhouse kitchen, with the kerosene lamp, the kettle on the stove and the ether mask made of newspaper and a hand towel. The marvel is that surgical results were so satisfactory under those adverse conditions.

In the second decade of the century, the impact of World War I molded surgical progress to its military needs. Stabilized trench warfare made prompt evacuation of the wounded practically impossible, and during major offenses, when the few roads were blocked by traffic and the wounded had only fourth priority, being superseded by men, ammunition and food, the patients reached the casualty clearing stations and evacuation hospitals in wretched condition. It was soon evident that even the minor wounded faced almost certain death if they were operated upon as they arrived, in profound shock from exposure and starvation after hours on the battlefield. Shock wards were established, and supportive measures instituted before operation was considered.

Transfusion of blood had been developing step by step previous to the war: the direct suture of donor artery to recipient vein, the cannula of Crile, paraffin tubes and, finally, citrated blood for indirect transfusion. In the preoperative ward transfusion proved its pre-eminent place in the treatment of shock. Blood substitutes were tried but were soon discarded as dangerous and ineffectual by comparison. In other fields of surgery, methods of treatment were developed that have stood the test of time. The adequate débridement of wounds, which in principle dates back to Larrey, Napoleon's great military surgeon, with removal of all devitalized tissue and foreign particles, was found to be essential. Delayed suture decreased the incidence of severe sepsis. Fractures were splinted on the field before transportation, to diminish the likelihood of shock and secondary injury to nerves and blood vessels. Head injuries were treated by removal of the foreign body and lacerated brain substance, under gentle and meticulous technic.

Grave defects in the handling of the wounded were demonstrated that were not rectified before the war's end. The most glaring of these was the inadequacy of transportation of the wounded. During times of stress with heavy casualty lists it was impossible to care properly for the wounded within the corps area in the zone of advance. Many walking wounded, with trivial injuries inadequately treated in the forward area, lost limb or life from being sent far back to the base on the hospital train. Gas gangrene had not been conquered. Abdominal and chest wounds were accompanied by an inordinately high mortality.

Before hostilities ceased one innovation in the military establishment, the Consultant Service, had so definitely proved its worth that when the storm clouds of the second World War broke twenty-three years later, the medical department at once reactivated and expanded it, although it has never been officially accepted in the tables of organiza-

tion. The duty of the Consultant Service, composed of well trained civilian doctors from the different branches of medicine, was to chart the course of treatment and supervise the professional care of battle casualties and personnel in the zone of advance, the service of supply and the base area overseas. The early antagonism of the regular medical officers gradually eased as they learned that the consultants were not trying to rob them of their administrative prerogatives. However, since the consultant had no official position and was delegated no authority, embarrassing and difficult situations often arose. He had to watch his actions and his words with far greater care than the United Nations diplomat.

On one occasion the chief surgeon of the First Corps ordered me to join the Eighty-Second Division on its first tour at the front. I turned in my orders at divisional headquarters, but the surgeon was apparently too busy to see me. After a couple of days of looking around I had some recommendations I thought might be worth while and by persistence got an interview. The colonel looked me up and down and said: "So you're a Consultant? There's no such grade as a Consultant and even if there was, my division doesn't need one." I was a bit nonplussed but had a happy thought and said: "The Corps surgeon didn't understand that, so if you will just endorse my orders telling him you don't need a consultant I will be glad to take them back to him and he will understand." Needless to say, the endorsement was never written, but our relations were none too cordial.

One fact was clearly demonstrated by the experience of the war. The young surgeon fresh from his residency quickly developed excellent judgment, a smooth, accurate operative technic and a facility for handling the cumbersome steps of the Carrel–Dakin treatment. This display of ability has led to placing more responsibility in his hands and giving him greater operative opportunity until today the resident staff in the larger teaching hospitals does the bulk of the ward surgery. In his year's service, the senior resident will do many gastric and colonic resections, some lobectomies and probably several esophageal resections and pancreatectomies. He will emerge from his training a fully qualified, adept surgeon. With unrest throughout the world and with the possibility of World War III before us, it is our obligation to give such training to our students. On their shoulders will be the burden of the care of casualties, military or civilian, should the disaster strike. We know by past experience that older doctors cannot stand the physical and mental strain of active military campaigns.

Prior to the war few group clinics had existed, but in the succeeding years they multiplied rapidly. Perhaps in small part because of the pioneering spirit unfettered by long-standing custom but probably as a result of environment, these groups sprang up largely in the Midwest and West, where centers of population with medical schools and teaching hospitals were widely separated. There are many advantages to patient and physician in group practice, although it seems that in part the close and important doctor-patient relationship is sacrificed. Complete coverage of diagnostic and laboratory procedures should be accomplished, with a saving of time and money to the patient. The same thing is true of the doctor in the conservation of time and the avoidance of duplication of equipment and personnel. At the present time, with the high cost of living, prohibitive taxation and the excessive financial burden of illness, monetary considerations for both patient and doctor must be given careful consideration.

In these post-war years the field of the general surgeon was narrowed by the growth of the specialties. No longer did he do a nephrectomy, and he was frowned upon if he set a broken leg. Today, the specialties are firmly established, but they have multiplied to the point where some of them are small splinters of the original broad plank of general surgery from which they were whittled. The unfortunate aspect of this trend is the early period in his training at which the young medical graduate branches off into his specialized field. It would be wise if the specialty boards required two full years of general surgery to lay a firm foundation before permitting him to embark on his specialized training.

The technical advances of this period lay first in the appreciation of the value of blood in preventing and combating shock, thereby increasing the magnitude and scope of surgical procedure. The Jutte and Levine tubes for gastric and duodenal drainage in ileus and obstruction, and for alimentation and fluid replacement in cases of depletion, altered the management of the preoperative and postoperative periods in gastrointestinal lesions. This era saw the passing of the surgical showman, with his deft but ruthless technic. Gentleness in the handling of tissues, conservation of blood and accuracy in the approximation of structures permitted more extensive procedures within the abdomen. The follow-up clinic revealed the failures, so that formerly accepted operations were being questioned and discarded — gastroenterostomy for peptic ulcer, for example, being gradually superseded by gastrectomy.

Refinements of diagnostic technic evolved. The cholecystogram and the intravenous pyelogram were important among the many laboratory tests applicable. No longer could the useful and familiar "exploratory laparotomy" be placed on the schedule of operations. It was a sign of diagnostic failure and brought the flush of shame to the surgeon's cheek when scrutinized by the astute resident or intelligent student. The life of the surgeon was growing harder.

Open surgical attack on the thoracic viscera dates from the late twenties. The stumbling block had been lung collapse and mediastinal shift, with its consequent train of symptoms. A few procedures had been done in the negative-pressure chamber of Sauerbruch, but it was not until modern intratracheal anesthesia became available that lobectomy and resection of mediastinal tumors were generally accepted. In the last twenty years awakened anesthesiology has placed at the disposal of the surgeon ethylene, cyclopropane, Pentothal continuous spinal anesthesia and the curare derivatives, to mention but a few of the anesthetics from which to choose for the particular case in hand. However, the fact that ether is the safest of all anesthetics must be ever present in our minds. Mechanical improvements have kept pace, with the introduction of the scientific anesthesia apparatus and the oxygen tent and mask.

Even before World War II the tempo of work in the research laboratories had increased, and results of fundamental importance in the care of the sick were made available to the clinician. Fluid and electrolyte requirements were determined so that a proper balance might be maintained. Hemorrhage in jaundiced patients, a bugbear to the surgeon for generations, was proved to be due to a reduction of prothrombin in the blood and was successfully combated with vitamin K. Heparin and later Dicumarol were efficacious in the treatment of thrombosis and embolism, and embolectomy for major circulatory obstructions was placed on the surgical map. The study of wound repair revealed the cause of delayed healing to be in foreign-body reaction, necrosis, infection and the accumulation of collections of serum or pus. The fallacy of the use of heavy material and too tight approximation of tissues, with consequent constriction necrosis, was evident. The silk technic or fine absorbable ligatures, both adequately strong in comparison to the tensile strength of the tissues, was generally accepted.

The employment of sulfanilamide, an appreciation of the importance of adequate preoperative preparation of the bowel and refinements of technic, such as aseptic anastomosis, diminished the danger of infection and allowed a more radical attack on gastrointestinal cancer by resection and suture, supplanting the formerly valuable and ingenious Mikulicz exteriorization. By producing alterations of physiology in an indirect rather than direct attack on disease, the surgeon invaded a new field in an effort to benefit or relieve the patient. Denervating procedures were used for the control of intractable pain, vasospasm, angina pectoris and hypertension among such attempts. Sympathectomy may not be the final answer in hypertension, for example, since the follow-up data have shown that the course of the disease is unaltered in many cases, but if patients are carefully screened and only those falling into certain categories are subjected to operation, good results may be anticipated.

By this time the gathering clouds of war had broken and conflict flamed across western Europe. Involvement of the nation in the struggle seemed imminent, and measures to place the country in readiness were taken. Yet when the blow fell with the dastardly attack on Pearl Harbor, as always in a democracy, we were far from prepared. Herculean effort was needed, and the medical profession responded nobly. Within a few months the number of medical officers in service leaped from 1300 to 40,000. It might well have been expected that such a vast influx would have led to a confusion disastrous to the proper care of the wounded and sick. Fortunately, the consultant service that had proved so valuable overseas in World War I was activated and expanded to cover all fronts overseas and all regional base areas in the United States. By careful scrutiny of their training, a truly remarkable job was done by the service in assigning men to positions where best they fitted. The lack of trained men in certain specialties appeared to present an unsurmountable obstacle. For instance, at the beginning of hostilities there were but 154 trained neurosurgeons in the whole country to care for both civilian and military needs. Intensive training in neurosurgical centers was given to recently graduated residents in general surgery. Though brief and concentrated these courses turned out over 200 capable young neurosurgeons, with the result that neurosurgical casualties received unprecedentedly good care. Had it not been that the recent resident group had had a splendid background in general surgery, such an intensive training in this and other specialties would have been impossible. It behooves us to see that our residents today receive even better training and greater opportunity.

I shall not dwell on the surgery of the war, for many of you know it far better than I by your own experience. Statistics in general are dry, but some comparative figures are so impressive that I cannot pass them by. The mortality of over 60 per cent in abdominal wounds in the first World War was more than cut in half in the second; chest wounds dropped from nearly 25 per cent to 8 per cent, and gas gangrene, a dreaded scourge in 1918, was rarely encountered.

What were the reasons for this dramatic improvement in the management of the wounded? The basic principles of military surgery, treatment of preoperative shock, débridement and delayed suture, learned in the first war the hard way by bitter experience, remained the same. Five causes can be assigned: the excellent quality of surgical care rendered the casualty far forward in the combat area by the well trained young surgeons; accelerated evacuation of the wounded, especially by plane; a better understanding of the management of shock, or resuscitation, as it came to be called, preopera-

tively and postoperatively; the use of chemotherapeutic agents and antibiotics; and finally, the availability of lavish amounts of blood and plasma. Never before had armies in conflict received such efficient surgical care.

In the years since the close of hostilities (I regret that I cannot say the establishment of peace) the lessons of the war have again influenced civilian surgery. The blood bank has been carried over into civilian practice, with its life-saving benefits. The chemotherapeutic agents and antibiotics have been of inestimable value to the surgeon performing potentially infective procedures and dealing with frank sepsis, and formerly prevalent infections such as mastoiditis and empyema requiring surgery are practically nonexistent today. The treatment of burns has undergone extensive modification. The scrubbing brush, tannic acid and even débridement have been discarded. Emphasis is placed on the correction of electrolyte balance, rapidly depleted by the outpouring of vital body fluid. The excessive protein loss is rectified by copious administration of plasma, and blood is valuable in hemolysis, though of less importance. Pressure dressings attempt to check the disastrous loss of serum. Antibiotics are given to diminish infection so that early grafting is feasible. Contractures are prevented by appropriate apparatus.

The transthoracic approach to subdiaphragmatic viscera — notably the stomach, spleen and kidney — is a recognized alternative approach. The surgery of the great vessels and heart has been stimulated. Obliteration of the patent ductus arteriosus, first successfully accomplished before the war, was but the forerunner of many curative procedures now undertaken to relieve congenital circulatory anomalies. Preserved arterial grafts and plastic tubes of various kinds have been utilized. The esophagus throughout its thoracic extent has been excised with gastric reconstruction.

What would Dr. Samuel D. Gross, dean of surgery in his era and founder and first president of the American Surgical Association, say of present-day surgery? In his welcoming address to the fellows at the meeting in Philadelphia in 1883 he said, "Operative surgery challenges the respect and admiration of the world; and if it has not attained its finality it is as nearly perfect as we can hope to make it." We would be as astonished if we could look at surgery fifty years hence as he would be today.

The record of surgery in the first half of the century is one in which we may well take pride. We must not settle into complacency, for there are many pressing questions that must be answered. Medical education is the longest and most expensive course offered today. Many highly intelligent and temperamentally fitted young men are forced to forego a medical career because the financial burden is overwhelming. Assistance to the properly qualified student by some form of governmental fellowship appears a necessity. Medical schools should lighten the premedical requirements or permit adjustments between school and college so that integrated courses leading to degrees in both institutions would be shortened by at least a year. The span in active practice and bread-winning opportunity is so short that every effort should be made to lengthen it but without sacrifice of educational standards.

A closer liaison between hospitals in larger teaching centers and surrounding communities should be fostered, whereby a beneficial interchange between the assistant resident grades for a limited period would be a regular part of the program. The young people of today are marrying at an earlier age than formerly. Young graduates in other professions such as the law are paid a living wage. Although the hospital assumes the obligation to instruct the resident and intern staffs, which is the main objective for seeking appointment, they on their part furnish a service without which the institution could not adequately function. A modest increase in remuneration would heighten the feeling of self-respect and instill a greater pride in performance of their duties.

The scarcity of nurses during the war has eased but slightly in the last few years. Steady employment, regular hours, assurance of a pension at the age of retirement and care of a congenial class of patients divert many recent graduates from civilian channels to the Veterans Administration. This is reflected in the shortage of beds in many institutions. Post-war expansion to create greater facilities has been rendered futile by the inability to staff the new wards. To meet the deficit three classes might be trained for nursing services: a one-year course for attendant nurses, fully capable of adequate service to the usual case; a two-year course sufficient for the registered nurse, available for specialized care in critical illness; and, finally, a three-year course for students of special aptitude and intelligence to be educated to assume administrative positions in hospitals or industrial plants.

The most momentous decision that medicine in the United States has had to face is before us now. Shall the care of the sick become a governmental function, a further expression of the socialized state toward which we are drifting all too rapidly? The cost of illness has reached fantastic heights, far too great to be borne by the individual. Shall we, as a people, allow the Government — appointed by us — to carry out our will within the law? Shall we allow the Government to usurp our freedom of choice and action? Or shall we meet the situation by a wisely considered far-seeing plan of sickness insurance universally applicable to all classes or workers in every field?

This has been but a brief and incomplete record of surgical progress as I have seen it unfold since the early years of the century. Of necessity many milestones have been skipped, and advances in allied branches of the profession have had to be ignored, though not for lack of appreciation of the achievements. That the pace of this splendid advance may not slacken, medicine must remain unshackled and free from political and governmental control. It must be permitted to carry on in the brilliant and progressive manner fundamental to the American way of life by the vital and investigative spirit of young doctors, whose training is unequaled in the world.

319 Longwood Avenue

PLASMACYTIC LEUKEMIA*

Report of a Case

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THE presence of plasmacytes in the peripheral blood of patients with multiple myeloma, particularly in the terminal stages of the disease, is a well known phenomenon. It is also recognized that multiple myeloma, on occasion, exists in a diffuse form throughout the bone marrow without the production of the usual nodular tumor masses causing local resorption of bone. The subject of this report is a case in which plasmacytic leukemia was the dominant form of the disease, clinically and pathologically, throughout its course.

CASE REPORT

W. S. (M.I.B.H. 40313), a 55-year-old foreign-born laborer, was admitted to the hospital on February 15, 1949, complaining of progressively increasing weakness of 3½ months' duration and bleeding from the gums and nose for 1 week prior to admission. No history of exposure to hematotoxic substances could be elicited. The onset of weakness and accompanying anorexia had been insidious; a low-grade fever had developed without chills or signs of localized infection. A physician administered penicillin and prescribed bed rest. After 2 weeks of this regimen, the patient returned to work for 4 weeks. His weakness persisted and increased. He was subsequently admitted to another hospital for 3 weeks, and it was reported that the red-cell count was 2,000,000 and that lymphoblasts were present in the blood smear. He received four transfusions of whole blood. After discharge he remained at home, becoming progressively weaker. He had lost about 12 pounds in weight since the onset of the illness. He had not noted hematuria or melena.

Physical examination showed a well developed, moderately well nourished, pale man in no acute distress. The conjunctivas were pale. The pupils were round and regular and reacted to light and to accommodation. The ocular fundi were pale, without other abnormalities. There was clotted blood in both nostrils, and blood oozed from the gums. A few small lymph nodes were palpable in the neck, axillas and inguinal regions. The lungs were clear. The heart was of normal size, with regular rhythm and without murmurs. The liver edge was palpated 6 cm. below the costal margin in the midclavicular line; it was firm and nontender. The spleen was also palpated 6 cm. below the costal margin and was also firm and nontender. Examination of the genitalia and rectum disclosed no abnormalities. The extremities presented no unusual features. Neurologic examination revealed no lesions. No petechial or other skin lesions were present.

The temperature was 99.4°F., the pulse 86, and the respirations 20. The blood pressure was 170/100.

The results of various laboratory studies are presented in Table 1. The red-cell counts were probably unreliable because of the marked tendency of the blood to undergo spontaneous agglutination and rouleaux formation. Erythrocytes in smears appeared to be microcytic and hypochromic, and there was also anisocytosis and poikilocytosis. Occasional nucleated rubricytes were seen. Peroxidase stain showed 72 per cent negative and 28 per cent positive cells on one occasion. The blood Wassermann test was unsatisfactory because of anticomplementary activity of the serum. Examinations of the urine showed it to be acid, with a specific gravity of 1.001 to 1.010. There were + to ++++ tests for protein, but Bence–Jones protein was not demonstrable on the three specimens tested. There was no sugar. The sediment showed occasional erythrocytes, rare white blood cells and rare hyaline casts. Occult blood was demonstrated in the stools (+ to +++ guaiac tests).

X-ray studies disclosed prominent but symmetrical venous channels in the skull, but there were no areas of bone destruction. The heart and lungs appeared normal. There was no enlargement of the mediastinal lymph nodes. The ribs, clavicles, scapulas, vertebras and pelvic bones showed no abnormalities. Both humeri and femurs were similarly free from roentgenologic evidence of destruction of bone.

The patient remained in the hospital 11 days and during that time received 2500 cc. of whole blood, with but a slight rise in the hemoglobin levels. He gradually improved symptomatically but continued to bleed from the nose and gums. The temperature rose occasionally to 100°F., and once to 101°F.

A biopsy of the sternal bone marrow was performed on the 4th hospital day. The specimen consisted of 10 fragments of soft, red bone marrow intermingled with spicules of cancellous bone. The average diameter of each fragment was approximately 0.2 cm. Microscopical examination revealed general replacement of the usual marrow component cells and destruction of the usual architectural pattern by a diffuse infiltration of cells characterized by a small, rounded hyperchromic nucleus in eccentric position, with dense chromatin material in typical cart-wheel arrangement. The cell cytoplasm was fairly abundant, dark and clear. Cell boundaries were distinct. Many cells appeared less mature, with less well defined characteristics of the plasmacyte, but apparent transition forms were recognized. Mitoses were present in moderate number. In a few areas residual islands of erythropoiesis and granulopoiesis were identified, and occasional megakaryocytes could be found. The biopsy was interpreted as showing leukemic infiltration of the bone marrow, plasmacytic type or diffuse plasmacytic myeloma.

The patient remained at home after discharge, gradually losing strength and with blood continuing to ooze from the gums and nose. He became semistuporous and had diffi-

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culty in breathing. He was readmitted to the hospital in extremis 12 days after discharge.

Physical examination showed the patient to be moribund; he was semistuporous and gasping for air. The blood pressure was 90/60, and the radial pulses were unobtainable. The skin showed a yellow pallor; the nail beds and lips were pale and gray. Rales were heard over the lung bases. Examination of the abdomen disclosed no new findings; there was no evidence of massive hemorrhage. The hematocrit showed 13 per cent erythrocytes and 9 per cent buffy coat. The patient died 41 minutes after admission.

Autopsy was performed 13 hours after death. Permission to examine the central nervous system was not granted. The wound of the sternal-marrow biopsy was well healed. There were areas of recent ecchymosis in the skin of the antecubital fossae and the lateral aspect of the left thigh; these were in relation to needle punctures. No other skin lesions were noted. There was dependent post-mortem lividity and generalized rigor mortis. The peritoneal surfaces were free from exudate.

TABLE 1. *Laboratory Data on First Admission.*

DATE	RED-CELL COUNT	HEMOGLOBIN	HEMATOCRIT	SEDIMENTATION RATE		WHITE-CELL COUNT	SEGMENTED NEUTROPHILS	MYELOCYTES	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	PLASMACYTES	PLATELETS
				INITIAL	CORRECTED								
	x10⁶	*gm./100 cc.*	*%*	*mm./hr.*	*mm./hr.*	*x10³*	*%*	*%*	*%*	*%*	*%*	*%*	*x10³*
Feb. 15	2.15	4.9	—	—	—	29.3	21	—	50	4	3	22	—
Feb. 16	2.68	6.0	16.9	78	13	38.5	20	—	49	5	1	25	52
Feb. 18	2.69	6.9	—	—	—	19.7	19	—	47	4	3	27	—
Feb. 23	2.0	4.6	—	—	—	13.3	15	2	51	4	1	27	—
Feb. 25	3.26	—	21.3	—	—	—	—	—	—	—	—	—	—

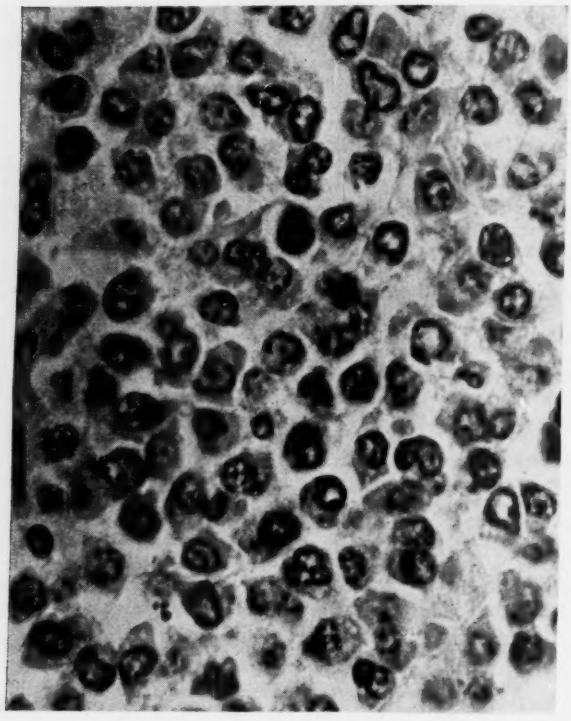

FIGURE 1. *Bone Marrow of Rib (Bullard's Hematoxylin and Eosin Stain x1000).*

There is a diffuse replacement and infiltration of the marrow by plasmacytes and proplasmacytes. Almost no normal marrow components are identifiable.

The lungs weighed 650 gm. each. The bronchi contained blood-tinged, frothy fluid. The lungs were subcrepitant throughout, and the dependent portions were airless. There was generalized pulmonary edema. No focal lesions were noted. The pleurae were not remarkable.

The heart weighed 375 gm., and all chambers were moderately dilated. The pericardium, epicardium and endocardium presented no abnormalities. The myocardium was slightly paler than normal. The valves and coronary vessels showed no abnormalities. There was minimal arteriosclerosis of the aorta.

The bone marrow of the ribs, as well as that of the vertebral bodies, was pale and grayish red. No focal lesions were identifiable grossly. No areas of destruction or tumor were seen in the ribs, vertebras or pelvic bones. The spleen weighed 450 gm. The capsule was tense, and the pulp was soft. Trabecular pattern and malpighian corpuscles were obscured. Tracheobronchial, mesenteric and retroperitoneal lymph nodes were slightly to moderately enlarged and firm, and follicular pattern was obscured in cross section.

The lips and buccal mucous membranes were pale. The gums were swollen and partially coated with clotted blood. The esophagus, stomach, small intestine, large intestine and appendix presented pale mucosal surfaces. The walls were of normal thickness. Peyer's patches were prominent.

The liver weighed 1900 gm. It was slightly paler than normal. It was of normal consistence, and no focal lesions were demonstrable in cross sections. The biliary system was unremarkable, as was the pancreas.

The kidneys weighed 150 gm. each and, apart from pallor, presented no abnormalities. The renal pelvis, ureters and bladder were unremarkable. The prostate weighed 60 gm. and was of normal consistence, without nodularity. The testes weighed 15 gm. each.

The thyroid gland was of normal size, shape and consistence. The parathyroid glands were not enlarged. The adrenal glands weighed 8 gm. each and showed no changes other than autolysis.

On microscopical examination of the lungs most of the alveoli were filled with the dense acidophilic protein precipitate of what appeared to be an edema fluid of unusually high protein content. The alveolar walls contained numerous plasmacytes, both within the capillaries and interstitially. There were rare foci of acute pneumonitis, with segmented granulocytes in the alveolar walls and in the air spaces.

In the heart, apart from numerous plasmacytes within the blood vessels, no significant findings were noted.

Sections of rib and vertebral bone marrow showed essentially the features previously noted in the surgically biopsied sternal marrow. There was extensive infiltration of the marrow with replacement of the usual structure by plasmacytes and immature forms of the plasmacytic series. Occasional Russell bodies were identified. Among the plasmacytes, rare megakaryocytes and rare cells of erythrocytic and granulocytic series were present. The infiltration by the plasmacytes and their apparent precursors was diffuse. No discrete, homogeneous nodules were encountered. Occasional hemosiderin-laden phagocytes were seen (Fig. 1).

There was generalized packing of the splenic sinusoids and infiltration of the pulp by plasmacytes. The lymphocytic elements of the malpighian corpuscles were markedly depleted so that these structures were obscured. There was plasmacytic infiltration and fragmentation of the outer layers

of trabecular connective tissue. Hemosiderin-filled phagocytes were moderately numerous (Fig. 2).

Tracheobronchial and retroperitoneal lymph nodes showed packing of vascular channels and sinusoids with plasmacytes with some obliteration of the normal architectural pattern. The capsules remained intact (Fig. 3).

The portal areas of the liver showed a moderate diffuse increase in plasmacytes, both intravascular and interstitial.

In the testes spermatogenesis was markedly decreased. There was interstitial edema. The blood vessels contained large numbers of plasmacytes.

In the prostate there was minimal stromal and glandular hyperplasia. No other abnormalities were noted apart from intravascular plasmacytes.

The thyroid gland was histologically unremarkable.

TABLE 1 (*Concluded*).

DATE	CAPILLARY BLEEDING TIME	VENOUS CLOTTING TIME	PROTHROMBIN INDEX	TOTAL SERUM PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN	SERUM URIC ACID	BLOOD UREA NITROGEN	ICTERIC INDEX	ALKALINE PHOSPHATASE	CEPHALIN FLOCCULATION	THYMOL TURBIDITY	FASTING BLOOD SUGAR
	min.	*min.*		*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		*King units*	*per 24 hr.*	*MacLagan units*	*mg./100 cc.*
Feb. 15	—	18	—	—	—	—	—	—	—	—	—	—	—
Feb. 16	8¾	—	0.76	10.7	1.2	9.5	10.6	57.4	—	—	—	—	104
Feb. 18	—	—	—	—	—	—	—	—	11	1.0	+++	14.8	—
Feb. 23	—	—	—	10.5	1.1	9.4	—	—	—	—	—	—	—
Feb. 25	—	—	—	—	—	—	—	—	—	—	—	—	—

There were occasional clusters of plasmacytes within the sinusoids.

Apart from intravascular plasmacytes, the pancreas showed no significant alteration.

Evaluation of the renal changes was rendered difficult because of post-mortem autolysis. Many of the convoluted tubules demonstrated so-called "colloid degeneration" of the tubular epithelium. There was marked protein precipitate within most of the convoluted and collecting tubules. In occasional glomeruli, the capillary basement membranes appeared slightly thickened and refractile.

DISCUSSION

The clinical features of this case were those of acute or subacute leukemia. No discrete tumor nodules were demonstrable roentgenologically, on physical examinations or at autopsy. The biopsy and autopsy findings were those of leukemic infiltration of the spleen, liver, lymph nodes and bone marrow by plasmacytes or their immediate

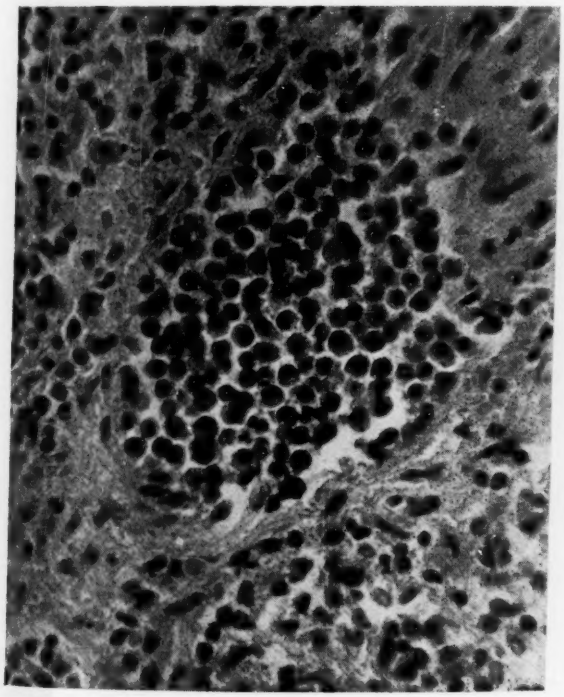

FIGURE 2. *Spleen (Bullard's Hematoxylin and Eosin Stain x460).*

A terminal vein is packed with plasmacytes and occasional proplasmacytes. The adjacent pulp is infiltrated by similar cells.

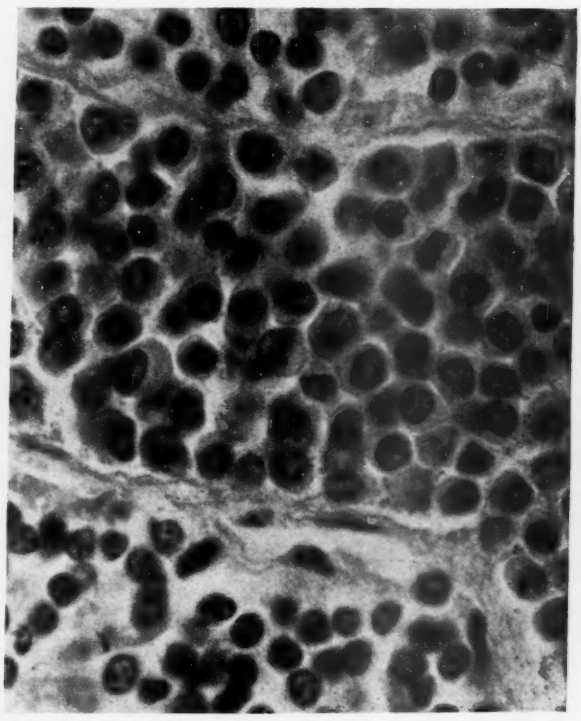

FIGURE 3. *Mediastinal Lymph Node (Bullard's Hematoxylin and Eosin Stain x1000).*

A medullary sinus is distended with plasmacytes. The surrounding pulp shows mature lymphocytes and occasional plasmacytes.

precursors. There was no evidence of Bence–Jones protein in the urine or of amyloidosis.

Recent reports of crystalline deposits, presumably protein in nature, in the renal tubules and in the tubular epithelium in cases of "diffuse plasmacytosis" and in multiple plasma-cell myeloma have come to our attention.[1, 2] Although true crystals were not identified in the sections of kidneys, bone marrow or spleen in the case presented above, it is of interest that granules or droplets with staining reactions similar to those of the crystals were present

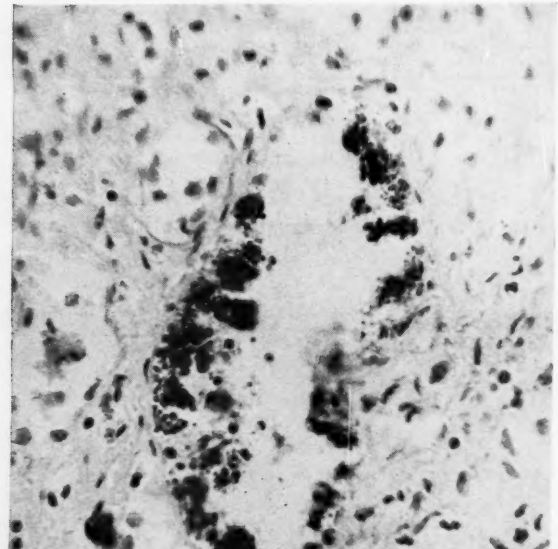

FIGURE 4. *Kidney (Weigert's Stain for Fibrin x425). The epithelial cells of this proximal convoluted tubule are filled with droplets. A few degenerated cells and their contents are present in the lumen.*

in the epithelial cells of many of the proximal convoluted tubules and occasionally in the casts within convoluted and collecting tubules. They stained bright red with Mallory's aniline blue method for connective tissue and deep violet in the sections stained for fibrin by Weigert's method. They were inconspicuous in sections stained with hematoxylin and eosin (Fig. 4).

Some doubt has been cast upon the existence of plasmacytic leukemia as a clinical and pathological entity although the presence of plasma cells in the peripheral blood has been described in many cases of multiple myeloma.[3, 4] Moss and Ackerman[5] consider the readiness with which plasmacytes enter the blood as an index of the malignancy of the neoplastic process; in support of this, they note that the average duration of life after diagnosis is two years in typical multiple myeloma but only eight months in "plasmacytic leukemia."

It seems established that the plasmacyte or its neoplastic variant is the characteristic cell of multiple myeloma.[4-8] The origin of the plasmacyte is less obvious. It has been variously considered to arise from the rubriblast,[9] the lymphocyte,[10] the lymphoblast,[11] the myeloblast[12, 13] and even intrinsic bone cells. The theory that the plasma cell is derived from the reticulum cells of the reticuloendothelial system now has fairly wide acceptance.[7, 14, 15] Thus, the plasmacyte is closely related to the lymphocytic series of free and fixed cells.

Certain analogies present themselves in the clinical and pathological behavior of neoplasms of plasmacytes to neoplasms of the lymphocytic series. It is possible to recognize cases apparently representing transitions from lymphoma to lymphatic leukemia.[16] A similar sequence could logically be expected in neoplasms of the plasmacytic series.

The similarities and differences between multiple myeloma and leukemia have been reviewed by Rubenstein,[17] who concluded that multiple myeloma is a "leukemia of plasma cells" usually occurring in the aleukemic form. This seems to us to represent an extreme point of view. However, we consider that the case presented above provides additional evidence for the existence of plasmacytic leukemia as a clinical and pathological entity and one that is an unusual but by no means illogical manifestation of a malignant neoplastic process of plasmacytes or their immediate precursors.

SUMMARY

A case that clinically and pathologically merits the diagnosis of plasmacytic leukemia is presented. The relation of this manifestation of the neoplasms of the plasmacytes to multiple myeloma is discussed.

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AUREOMYCIN IN THE TREATMENT OF THE COMMON COLD

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BECAUSE of the effectiveness of aureomycin in the treatment of primary atypical pneumonia of unknown etiology, often called virus pneumonia, and on many bacterial and nonbacterial microorganisms, an investigation, under controlled conditions, of its effect on the common cold appeared desirable. No such study has been reported, but Finland and his associates[1] stated that 10 patients with acute respiratory disease appeared to benefit from the use of aureomycin. These patients did not have pneumonia or influenza; 3 had tonsillitis or nasopharyngitis, and 7 could be classified as having a common cold or "undifferentiated acute respiratory disease" or "clinical influenza." Herrell,[2] in an article on the clinical use of aureomycin, stated that this antibiotic was ineffectual in the treatment of the common cold, but his statement was unsupported by references or data. Further impetus to this study was given by a failure to confirm the favorable reports of other investigators regarding the effectiveness of antihistamines in the treatment of the common cold.[3]

Any form of treatment for the common head cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible will provide results on which relatively valid conclusions can be based. Some of the variables are suggestibility of patients and also their physicians; fluctuation of a person's degree of immunity; difficulty of objective diagnosis of a head cold; unreliability of subjective impressions of a developing head cold until clear-cut symptoms, such as "sniffles," occur — and even then the patient may have some other disease, such as vasomotor rhinitis; the variable course of a head cold; the difficulty of follow-up examinations in a relatively trivial, spontaneously curable and self-limited disease; and variations in age and general health of patients.

Some of these factors merit further discussion. Fluctuations of immunity were discussed by Andrewes[4] in his Dunham Lectures at Harvard Medical School. He concluded that almost everyone has his own foolproof technic for preventing or curing colds, yet colds are as numerous and as troublesome as ever: "even the most eminent men of science almost invariably lose all sense of critical judgment when colds and especially their own colds are concerned." The spontaneous variation of duration of head colds was shown by Diehl,[5] who found that 35 per cent of patients with colds receiving lactose reported good results; he stated that this large percentage was the reason that it is easy to convince the public that almost any treatment for colds is of value. He found that some of his reports from persons receiving lactose would have made excellent testimonials for this inert material. He concluded that a combination of codeine and papaverine gave "definite improvement" to 74 to 78 per cent of patients. However, Brewster,[6] using this preparation, reported cure in only 31 per cent of 22 patients treated within twelve hours, and none of 50 patients who started treatment after symptoms had been present twenty-four hours. Diehl stated that the use of sodium bicarbonate, lactose and aspirin was followed by "definite improvement" in 35 to 42 per cent of cases. A significant observation was that as the winter progressed colds tended to become more severe, and in May all medicines used resulted in decreased reports of "definite improvement."

MATERIALS AND METHODS

The aim of this investigation was to eliminate as many variables as possible. The study was confined to healthy young males in the military service. Medical attention was rendered before duties began, eliminating the temptation to seek needless medical attention to avoid onerous duties. Personal prejudice was lessened because the medical officers pre-

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scribing treatment and doing follow-up examinations were unaware of what medicines the patients were receiving.

Pharmacists dispensed aureomycin* and inert yellow capsules* in rotation and recorded the necessary protocol in a ledger. Patients were encouraged to report for medical attention as soon as possible, and we noted particularly the effect on local and constitutional symptoms, the development of thick nasal discharge, the duration of this cold compared with the average length of a cold for the patient and the occurrence of undesirable side effects.

It was not practicable to attempt, in this study, to see the patients within the first few hours of a cold, and so they were instructed to report to the first sick-call formation following the onset of a cold. Thus, patients with transient, misleading symptoms, really not manifestations of head colds, were less likely to be included in this investigation. Furthermore, patients who seek a physician's attention for colds usually do not do so within the first few hours of the onset of symptoms. It was believed that only personal follow-up study, which continued over seventy-two hours, could be relied on for an accurate appraisal of the results of treatment. Therefore, patients were seen by us personally on either two or three occasions after the initial visit; however, all patients were seen seventy-two hours after treatment was begun.

TABLE 1. *Results of Treatment of the Common Cold.*

RESULT	PATIENTS RECEIVING PLACEBOS	TOTAL PATIENTS RECEIVING AUREOMYCIN	PATIENTS RECEIVING 1 GM. OF AUREOMYCIN DAILY	PATIENTS RECEIVING 2 GM. OF AUREOMYCIN DAILY
No benefit.....	51 (32.9%)	39 (25.3%)	15 (21.7%)	24 (28.2%)
Slight improvement	35 (22.6%)	48 (31.2%)	19 (27.5%)	29 (34.1%)
Moderate improvement ...	54 (34.8%)	51 (33.1%)	28 (40.6%)	23 (27.1%)
Cure in 24 hr. ..	15 (9.7%)	16 (10.4%)	7 (10.2%)	9 (10.6%)
Totals	155	154	69	85

RESULTS

This study of 309 patients with head colds disclosed that cures within twenty-four hours were reported by 10.4 per cent of 154 patients given aureomycin orally, but 9.7 per cent of 155 patients receiving placebos also reported cures. Other data concerning effects are reported in Table 1.

Figure 1 graphically shows the results of this study. It is apparent that patients receiving placebos by mouth fared about as well as those taking aureomycin. After 69 patients had been treated with 250 mg. of aureomycin four times daily, and results appeared to be unimpressive, it was decided to give 500 mg. four times daily to the next 85 patients receiving the antibiotic. Figure 1 discloses that patients receiving 1 gm. of aureomycin daily and those receiving 2 gm. had the same proportion of cures (10.2 and 10.6 per cent, respectively).

Inasmuch as making clear-cut distinctions between degrees of help and deciding on just when symptoms ceased or lessened is difficult for both patient and physician, we thought that grouping the effects obtained slightly differently might be informative. Therefore, patients who received no benefit or reported slight improvement were grouped together, as were those who reported either cure in twenty-four hours or moderate improvement. Again,

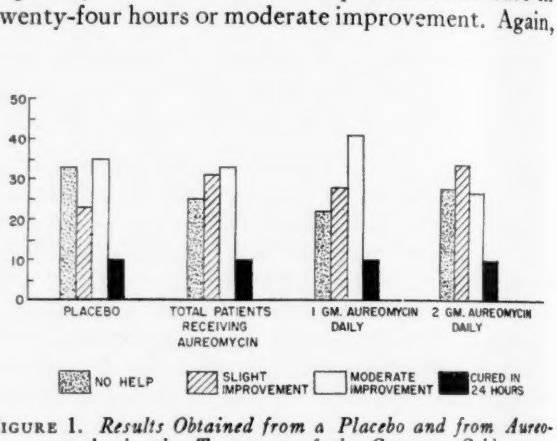

FIGURE 1. *Results Obtained from a Placebo and from Aureomycin in the Treatment of the Common Cold.*

no significant differences were observed. The slight differences between results obtained with smaller and larger doses of aureomycin may have been influenced by the fact that the different doses were used consecutively, not concurrently.

DISCUSSION

The broad range of antimicrobial action of aureomycin stimulated us to attempt to appraise its value in the treatment of the common cold. Although this study was carefully controlled and as many variables were eliminated as possible, it was our belief that only if the results were negative could valid conclusions be drawn. Unfortunately, and unavoidably, diagnoses and results of treatment had to depend somewhat on patients' statements. Apparently favorable results would have served chiefly as a stimulus to further confirmatory work in this field. The concomitant use of controls was necessary since immunity fluctuates and since head colds may be due to different organisms with varying virulence at different times of the year. Consequently, the proportion of cures obtained in December may be quite different from that obtained in May, as shown by Diehl.[5]

A noteworthy result of this investigation is that practically identical proportions of aureomycin-treated and placebo-treated patients reported cures in twenty-four hours. The results of this study corroborate the belief expressed in a study on the use of

*Kindly supplied by Lederle Laboratories, Pearl River, New York.

antihistamines in the treatment of colds[3] — namely, that spontaneous recovery of patients with colds occurs so frequently that enthusiastic conclusions regarding effects of treatment must be based on unassailable evidence. In this study about half the patients reported great or moderate help derived from inert material.

Conclusions

The necessity of a carefully controlled clinical investigation of treatment of the common cold is again demonstrated since in this investigation about half the patients receiving inert material reported either moderate improvement or a cure within twenty-four hours.

There was no significant difference in the proportion of cures reported by patients with colds receiving aureomycin and by those receiving a placebo. Furthermore, essentially the same proportion of patients treated with aureomycin and placebo reported slight or no benefit from either type of treatment.

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THE EFFECT OF WATER-SOLUBLE PREPARATIONS OF VITAMIN K IN DICUMAROL-INDUCED HYPOPROTHROMBINEMIA*

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IN THEIR pioneer studies of the sweet-clover disease in cattle both Schofield[1] and Roderick[2] observed that the hemorrhagic state could be reversed by a change in the diet, and particularly by the addition of alfalfa hay, which has since been shown to be rich in vitamin K. Quick[3] later noted a similar response in rabbits and chicks, but failed to relate this change to vitamin K. Link and his associates[4] were the first to demonstrate in animals that it was necessary to administer 2-methyl-1, 4-naphthoquinone, a form of vitamin K, in large doses in order to prevent the hypoprothrombinemia induced by Dicumarol. Shortly after this the same observation was made in man by Shapiro, Redish and Campbell[5] in this country and by Lehmann[6] in Sweden. Prompt confirmation was reported by Davidson and MacDonald,[7] and a dosage level of menadione bisulfite (Hykinone) to be used clinically to counteract excessive hypoprothrombinemia induced by Dicumarol medication was recommended by Cromer and Barker.[8]

Vitamin K is available on the market for parenteral use in water-soluble form. Recently, it has been claimed that the less soluble forms K_1 and K_1 oxide are effective, but that the water-soluble preparations of vitamin K are without activity in reducing excessively prolonged prothrombin time after Dicumarol therapy.[9, 10] It has been claimed that the phytyl group in the K_1 compounds is essential.[9]

The apparent inconsistencies in the reported response of Dicumarol-induced hypoprothrombinemia to water-soluble vitamin K may be resolved in part, at least, by a study of the recent investigations correlating the concentration of Dicumarol in plasma with the prothrombin time.[11, 12] These studies suggest that excessive hypoprothrombinemia following Dicumarol therapy may result from two mechanisms and that these may respond differently to vitamin K.

It has been established that the height and duration of the concentration of Dicumarol in plasma following a given oral dose vary widely in different persons.[11, 12] This is due not only to inconstancy in rate and completeness of absorption but also to the variable rate at which the drug is metabolized in different persons. Thus, a daily dosage that yields ineffective levels of Dicumarol in plasma in one person may result in an accumulation to excessively high levels in another.[11, 12]

It has also been established that subjects may vary widely in prothrombin response to a given concentration of Dicumarol in plasma. "Sensitive" patients may exhibit marked hypoprothrombinemia in response to plasma levels of 10 mg. per liter, whereas less sensitive persons may show only slight hypoprothrombinemia after plasma concentrations of 30 mg. per liter.

Thus, excessive prothrombin response to Dicumarol may result from marked accumulation of the drug in the plasma over a number of days or exaggerated sensitivity of the prothrombin-elaborating mechanism to relatively low and short-lived concentrations of Dicumarol in plasma. The data reported below demonstrate that a single large dose

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of a water-soluble preparation of vitamin K is usually adequate to correct the latter type of hypoprothrombinemia, and that patients with persistent high concentrations of Dicumarol in the plasma may require repeated large doses of water-soluble vitamin K to reduce to a safe level and control excessive prolongation of the prothrombin time.

Methods

Estimation of the prothrombin time was made by the Link–Shapiro modification of the one-stage method using standardized thromboplastin.* [12]

Determination of the concentration of Dicumarol in plasma was by the method of Axelrod, Cooper and Brodie.[13] The normal values of prothrombin time are: whole plasma, 15 seconds ± 1.5; and diluted (12.5 per cent) plasma, 37.5 seconds ± 2.5.

Results

Four patients (A, B, C, and D in Table 1) receiving Dicumarol medication exhibited excessive prothrombin responses that persisted for more than five days after the last dose despite low (A, B, and C) or moderate (D) concentrations of Dicumarol in the plasma. In each case a single dose of water-soluble vitamin K administered intravenously was followed by a reduction of the prothrombin time to within a safe range within twenty-four hours (Fig. 1).

Patients E, F, G and H (Table 1) exhibited high elevations of the prothrombin time accompanied by high or moderate concentrations of Dicumarol in plasma, owing either to repeated "maintenance" doses or to slow transformation of the drug following cumulation to a high level. The relevant features of each are presented below, and the data are summarized in Table 1.

Table 1. *Prothrombin Responses to Dicumarol Administration.*

Patient	Interval after Initial Dose of Vitamin K	Dosage of Vitamin K*	Dicumarol Plasma Concentration	Plasma Time	Prothrombin Time
				whole	diluted 12.5%
	hr.	*mg.*	*mg./liter*	*sec.*	*sec.*
A	0	75 (S)	4.5	50	150
	15			29	106
	40		3.6	22	49
B	0	75 (S)	5.0	35	101
	5			33	98
	25		3.2	24	48
C	0	112 (H)	8.4	86	217
	5		7.8	41	106
	17		5.8	34	70
	70		0	25	39
D	0	75 (S)	19.6	46	181
	24		15.9	30	84
	48		13.5	24	51
	72		—	18	43
E	0	144 (H)	28.0	22	54
	9	144 (H)	—	23	58
	24	—	28.0	21	48
	48	144 (H)	23.0	30	85
	58	144 (H)	—	—	—
	72	144 (H)	21.0	22	61
	96	—	17.0	17	54
F	0	75 (S)	—	60	264
	14	75 (S)	23.0	48	218
	23	75 (S)	—	34	93
	34	75 (S)	14.0	20	54
G	0	75 (S)	49.8	34	136
	5	75 (S)	—	—	—
	17	75 (S)	47.0	31	79
	89	—	26.5	27	73
H	0	72 (H)	12.9	35	108
	27	72 (H)	9.6	34	102
	48	72 (H)	14.0	27	69
	52	72 (H)	16.9	—	—
	72	72 (H)	15.1	26	65
	78	72 (H)	18.6	—	—
	96	—	17.2	16	46
	168	—	19.6	25	64
	192	—	18.0	30	86
	240	—	21.2	36	125

*H = Hykinone; S = Synkayvite.

Case Reports

E, a 62-year-old man with acute coronary thrombosis, received 300, 200 and 100 mg. of Dicumarol on the 1st, 2nd and 3rd days respectively. The drug was then withdrawn, but the prothrombin time continued to increase daily until the 7th day, when it became markedly extended and diffuse bleeding appeared. This was controlled by blood transfusion and intravenous injection of 72 mg. of menadione bisulfite (Hykinone). Five weeks later the present study was undertaken; 300 mg. of Dicumarol was given in one dose orally. The initial prothrombin times were as follows: whole plasma, 17 seconds, and diluted (12.5 per cent) plasma, 37 seconds. Eighteen hours later these were increased to 22 seconds and 54 seconds respectively. The plasma concentration of the drug was 28 mg. per liter. Hykinone was administered as shown in Table 1, and the prothrombin time demonstrated no further increase in 24 hours. No vitamin K was given during the following 24

*Kindly supplied by Maltine Company, Division of Chilcott Laboratories, Morris Plains, New Jersey.

hours, and the prothrombin time again increased. Hykinone was once more administered, and again the prothrombin time became reduced until the concentration of Dicumarol in the plasma fell to ineffective levels.

F, a 55-year-old woman with acute thrombophlebitis of the left lower extremity, improved promptly after the administration of Dicumarol. Fourteen days after the drug had been withdrawn, the patient slipped and fell on a concrete walk, and a massive hematoma of the right thigh developed. Interrogation elicited the admission that she had been taking "an occasional capsule" of Dicumarol of her own volition. The prothrombin time was found to be markedly prolonged — 60 seconds in whole plasma and 264 seconds in the diluted (12.5 per cent) plasma. Moderate levels of Dicumarol were found in the plasma. Three doses of water-soluble vitamin K (Synkayvite) of 72 mg. each were administered intravenously within 23 hours. The prothrombin time fell from the initial 60 seconds in whole plasma and 264 seconds in diluted (12.5 per cent) plasma to 20 seconds and 54 seconds respectively in 34 hours. The concentration of Dicumarol in the plasma was 14 mg. per liter. There was no further evidence of bleeding, and the subsequent clinical course was uneventful.

G, a 45-year-old man, was incapacitated because of neurologic disease. Because of his limited activity his metabolic and physical states were easily standardized. We had studied the prothrombin response to Dicumarol on a number of previous occasions. He had been found to be persistently insensitive to the drug, requiring high plasma levels of Dicumarol to induce therapeutically active hypoprothrombinemia. On the occasion of the present study he was receiving moderately large daily doses of Dicumarol, and the plasma level cumulated to a peak of 49.8 mg. per liter at a time when the prothrombin time was found to be at a high therapeutic level. Since the pattern of the prothrombin curve always follows that of the plasma Dicumarol levels by 1 or 2 days, and since the concentration of the drug in the plasma had been increasing up to that date, the prothrombin time was expected to rise farther. Three doses of water-soluble vitamin K given intravenously effectively prevented this elevation, allowing the concentration of the drug in the plasma to decline to safer levels without producing excessively high prolongation of the prothrombin time.

H, a 40-year-old man, was incapacitated by chronic neurologic disease. Previous studies had demonstrated him to be moderately sensitive to Dicumarol. On two earlier occasions he had exhibited excessive hypoprothrombinemia in response to plasma levels of 25 and 35 mg. per liter. Five days before the beginning of the present experiment the concentration of the drug in the plasma was 28 mg. per liter. Dicumarol was withdrawn, but the prothrombin time remained at a high level in spite of a gradual fall in Dicumarol plasma concentration of 12.9 mg. per liter. At this time Hykinone was given as shown in Table 1, and daily administration of 50 mg. of Dicumarol orally was resumed. Despite a rise in plasma levels of Dicumarol during the succeeding 4 days, the prothrombin time became reduced from 35 seconds in the whole plasma and 108 seconds in the diluted (12.5 per cent) plasma to 16 seconds and 46 seconds respectively. Administration of vitamin K was discontinued, and the prothrombin time again rose to high values.

Discussion

The experience has been almost universal among clinicians that water-soluble preparations of vitamin K are effective in reducing excessive Dicumarol-induced hypoprothrombinemia to a safe level. In dealing with a physiologic mechanism such as the elaboration of prothrombin numerous variables that are difficult to estimate must be taken into consideration. The functional capacity of the liver, the available store of building blocks for prothrombin synthesis and other intangibles are all factors in determining any patient's response to vitamin K. That some patients exhibit more dramatic responses

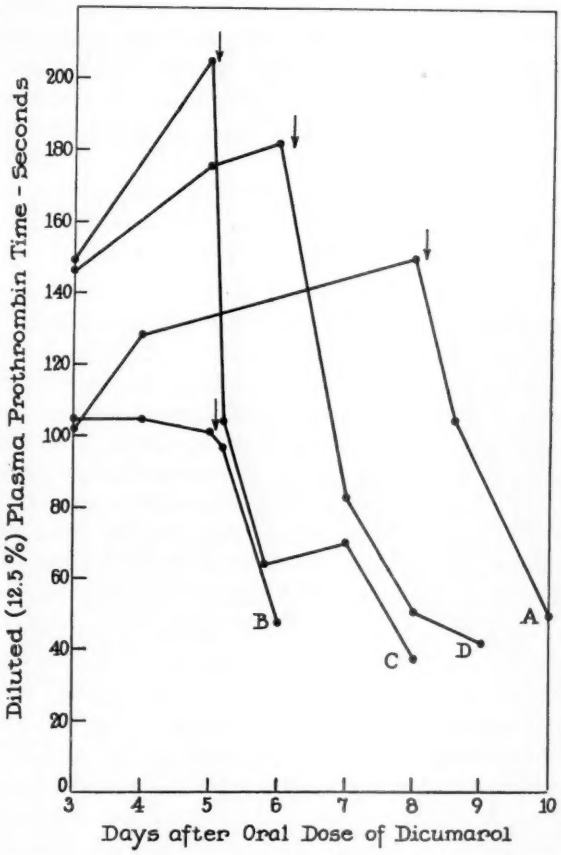

Figure 1. *Response of Subjects with High Prothrombin Time and Low Plasma Dicumarol Concentrations to a Single Does (Arrows) of Water-Soluble Vitamin K Intravenously.*

than others, and that occasionally the prothrombin time remains unaltered after a single large dose of water-soluble vitamin K is common experience among active workers in the field. In most of the reports of investigations in man that appeared before the publication of the study by Shapiro, Redish and Campbell[5] failure of response after vitamin K was recorded.[14, 15] It is now known that the doses of vitamin K used were inadequate. In the more recent paper,[9] in which ineffectiveness of water-soluble preparations of vitamin K was emphasized, only a single dose of these preparations was administered parenterally, while the concen-

tration of Dicumarol in the plasma was being maintained by continued daily doses of the anticoagulant. Obviously, this is not a reproduction of the situation as it might occur clinically. One would not administer further doses of Dicumarol in the presence of excessively prolonged prothrombin time. Our data demonstrate that after withdrawal of Dicumarol marked hypoprothrombinemia consequent to hypersensitivity of the prothrombin-elaborating mechanism to the drug can be readily reduced to a safe level by a single dose of water-soluble vitamin K preparation, and that hypoprothrombinemia related to high, maintained concentrations of Dicumarol in the plasma can be restored to a safe level by *repeated* doses of water-soluble vitamin K.

In the studies on the physiologic disposition of Dicumarol in the body[11] it has been observed that if a second dose of Dicumarol is given before the previous dose has disappeared from the plasma the new peak concentration in the plasma will be greater than the simple addition of the first peak to the level at the time of administration of the second dose. Therefore, a repetition of doses may summate at a rate greater than would be anticipated from the observation of the one-dose transformation rate. Since the prothrombin time responds twenty-four to forty-eight hours after the plasma level is achieved, added doses may accumulate in the plasma to an excessive level and induce bleeding five or six days later, as in patient E. If, instead one gives initially a single large dose adequate to induce the desired degree of hypoprothrombinemia and the prothrombin response observed, the danger of undetected cumulation can be more readily avoided. In this way the emergent necessity for vitamin K is much less frequent, since subsequent doses of Dicumarol are not given until it is certain that the peak response to previous doses has been achieved. A method of intermittent administration of large doses in place of the so-called maintenance-dose method, in which daily small doses are given, has long been employed by us, and probably because of greater predictability of the prothrombin time pattern, has been found safe and therapeutically effective.[12]

The rate at which Dicumarol disappears from the plasma is not altered by vitamin K at any dosage level. It appears that the role of vitamin K in prothrombin synthesis is interfered with by Dicumarol, possibly by a competitive mechanism. The presence of vitamin K in high concentration may overcome Dicumarol competition. Since the plasma concentration of Dicumarol may continue high for a considerable period, vitamin K must necessarily also be continued and at a high dosage level. Consequently, repetitive administration of the more rapidly disposed of water-soluble form of vitamin K is required. In situations with persistent high Dicumarol plasma levels, it is to be expected that the more slowly disposed of water-insoluble K_1 or K_1 oxide in very large doses[9] may exert a more pronounced and better sustained protective effect than single doses of the water-soluble preparations.

Adjustment must be made in the administration of water-soluble preparations of vitamin K to overcome excessive Dicumarol-induced hypoprothrombinemia so that large doses are given at intervals of six to twelve hours, depending upon the needs of the patient. In the event of active bleeding, blood transfusion and vitamin K are indicated. This will restore essential plasma proteins depleted by hemorrhage and counteract the uncertain influence of shock phenomena upon the coagulation mechanism. In the absence of bleeding and when it is not necessary to correct the coagulation defect immediately, parenteral administration of water-soluble vitamin K at high dosage level is an adequately effective measure for reduction of excessive hypoprothrombinemia to a safe level.

Summary and Conclusion

Four patients exhibiting excessive prothrombin responses with low concentrations of Dicumarol in the plasma showed reduction of the prothrombin time to a safe level within twenty-four hours of a single dose of a water-soluble preparation of vitamin K.

Four patients presenting high elevations of prothrombin time accompanied by high concentrations of Dicumarol in the plasma responded to repeated doses of water-soluble vitamin K by return of the hypoprothrombinemia to a safe level.

Water-soluble vitamin K is effective in controlling excessive Dicumarol-induced hypoprothrombinemia.

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MEDICAL PROGRESS

NUTRITION AND DISEASE OF THE LIVER*

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THE pathogenesis and therapy of liver disease are considered in some measure nutritional problems. The purpose of this paper is to survey the evidence implicating nutritional deficiency in the etiology of liver disease in man and contrariwise to point out the effects of established liver disease upon nutrition. Finally, the therapeutic implications derived from the facts available are presented.

The discussion is largely confined to the problems as they concern liver disease in man. Although animal studies are the origin of most of the fundamental knowledge, only a small fraction of the literature germane to such studies is included. Since nutrition involves the ingestion, digestion and absorption, intermediary metabolism and excretion of essential and nonessential nutrients, the discussion that follows is presented in this sequence.

NUTRITION IN THE PATHOGENESIS OF LIVER DISEASE

Deficient Food Consumption

Simple starvation or undernutrition rarely causes liver disease. For example, jaundice and other evidences of hepatic disturbance were not prominent in the European prison camps of the last war unless epidemic hepatitis occurred.[1, 2] In contrast, a higher incidence of liver disease was observed in repatriated prisoners of war from the Pacific Theater, many of whom had suffered from beriberi, pellagra, scurvy or xerophthalmia and whose diets were qualitatively more deficient than those in Europe.[3] Evidence from many parts of the world suggests a similar relation between malnutrition and liver disease, especially in the areas in which food consumption is abnormal in quality. The intense fatty liver found in patients with "infantile pellagra" in South Africa is another case in point, since maize forms the staple food for these persons whereas fat, calories, vitamins and particularly animal protein are deficient.[4] Moreover, cirrhosis of the liver occurs years earlier in these African pellagrins than in those without this disease. Incidentally, cytosiderosis or hemochromatosis frequently complicates this condition. Malignant malnutrition or "kawashiorkor" described in natives of central Africa is characterized by a fatty liver in addition to skin depigmentation, edema, diarrhea and anemia.[5] A similar syndrome occurs in India,[6] in the British West Indies[7] and in Peru[8] and often leads to cirrhosis, but not hemochromatosis. Laënnec's cirrhosis associated with faulty diet is also seen in patients in Ceylon.[9] In fact, cirrhosis of the liver is a widespread disease in parts of the world where diets are deficient, especially in animal protein. The complicating factor of infestation of the liver with parasites has not always been considered in the etiology of the liver disease in these patients.

The relation of diet to the genesis of "alcoholic" cirrhosis in Europe and America is still a matter of dispute, although a deficient diet probably contributes to the pathogenesis of the disease. However, liver injury may be produced by alcohol or some substance present in alcoholic beverages — for example, copper.[10] The specific dietary aberrations of chronic alcoholism are little known although those who drink steadily every day for years and reduce their food intakes only moderately more

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commonly develop cirrhosis of the liver with fibrosis than those who drink in sprees that are usually associated with almost complete abstinence from food.[11]

The extent of liver damage following exposure of animals to hepatotoxins such as carbon tetrachloride is greater if impaired nutrition is present.[12] Whether or not this is so in man is uncertain, but a nutritious diet is advocated for those possibly exposed to hepatotoxins.[13]

Infectious hepatitis and homologous serum jaundice are caused by filtrable viruses. Inadequate nutrition, according to some, serves to increase severity, prolong convalescence and increase the incidence of chronic hepatitis and post-hepatitis cirrhosis. Patients undernourished at the onset of an epidemic of infectious hepatitis during World War II appeared to have more severe disease than those who were well nourished, and, furthermore, patients who failed to gain weight suffered protracted courses.[14] Protein deficiency was considered the important factor. Similarly, the malnourished Indian troops had a far higher mortality from infectious hepatitis than British soldiers stationed in the same area, even though the incidence of the disease was higher in the latter group.[15]

Dietary deficiency of such "lipotropic" substances as lipocaic, methionine, choline, inositol and animal protein causes fatty liver and cirrhosis in animals under certain conditions.[16, 17] The evidence relates these events to a defect in phospholipid synthesis by the liver that accumulates fat in large amounts. Phospholipid synthesis is stimulated by administration of choline or of methionine, the latter providing methyl groups for the synthesis of choline. This fundamental work does not specifically indict deficiency of any of these nutrients in the pathogenesis of liver disease in man although, as pointed out above, improper food consumption unquestionably plays an important role. Generally, diets of persons in whom fatty liver and cirrhosis develop, whether associated with alcoholism or not, are, as noted above, deficient in protein, especially that of animal origin. This deficiency includes methionine, choline and the other nutrients usually classed in the vitamin B complex. The evidence incriminating dietary factors in the pathogenesis of liver disease in animal experiments is necessarily more specific than that in man, but the two bodies of evidence are compatible.

Defective Digestion and Absorption

Deficiencies of certain essential nutrients might arise not only directly from ingestion of inadequate food but also from such conditioning factors as impaired digestion and absorption. However, there is little evidence that the latter are etiologically important in liver disease in man.

Clinical evidence of nutritional deficiency resulting from defective absorption of nutrients does occur in patients with chronic diarrheal diseases such as sprue, celiac disease, regional ileitis, ulcerative colitis and gastrointestinal anastomoses. Nevertheless, severe liver disease is infrequently associated with these disease states although minor degrees of fatty infiltration do occur. However, fatty infiltration and fibrosis of the liver are sometimes marked in ulcerative colitis.[18-20] In one study decreased hepatic function was found in approximately half of 70 patients with ulcerative colitis although only 2 of the 11 patients autopsied had definite fibrosis. The liver disease that occurs in ulcerative colitis may be due to impaired absorption of nutrients attributable to prolonged and persistent diarrhea, although this thesis does not explain why diarrhea from other causes is not more commonly complicated by hepatic disease. Moreover, patients with established cirrhosis occasionally develop ulcerative colitis. The etiologic relation in these cases is even more obscure.

Abnormal Intermediary Metabolism

Liver disease might be expected to arise from an altered intermediary metabolism of nutrients as well as from reduced ingestion, digestion or absorption. Evidence of such a pathogenetic relation is difficult to establish, although liver injury may complicate several of the diseases of metabolism.

Fatty infiltration of the liver occurs in some patients with diabetes mellitus and may be marked although reports concerning its incidence and the occurrence of fibrosis vary greatly.[21, 22] Increased use of liver biopsy and the development of more sensitive and accurate liver-function tests may help to clarify this problem. A recent report of liver biopsies in 22 cases of diabetes revealed fatty infiltration or portal cirrhosis in 15.[23] Increase in glycogen content, also reported, may account for some of the cases of enlargement of the liver observed clinically in diabetic persons.

Dogs in which diabetes develops after pancreatectomy regularly manifest fatty livers and subsequent fibrosis even if maintained on insulin.[24] These hepatic changes may be prevented by the oral administration of whole pancreas, lipocaic (an extract of pancreas), choline, methionine or hydrolyzed protein. Whole protein does not prevent such changes. The pathogenesis of this condition is similar to that of the animals in which fatty livers develop from the direct dietary deficiency of choline and methionine that was discussed above, except that the depancreatized animals become deficient in spite of a diet adequate in whole protein. An important etiologic factor in the depancreatized animals appears to be lack of the external pancreatic secretion leading to impaired digestion and absorption of protein.[25] Doubt is entertained that a similar sequence of events occurs in diabetes mellitus

in man since there is no deficiency of pancreatic digestive enzymes in this disease.

A recent study of 115 cases of cirrhosis of the liver revealed 12 with diabetes mellitus.[26] Most of these had diffuse fibrosis of the pancreas, although classic hemochromatosis was present in only a few. It was suggested on the basis of these studies that the distinction between pigment and nonpigment cirrhosis may not be as abrupt as is usually thought. Studies such as these, together with the interesting pathogenetic sequence noted above of fatty liver, cirrhosis, and hemochromatosis in South African pellagrins, make the relation of nutrition to pigment cirrhosis an important one for further investigation.

Pathological evidence of hepatic disease occurs in thyrotoxicosis, and it is suggested that the changes (chiefly vascularity and fibrosis) are due to an increased hepatic blood flow in this disease.[27] The glycogen and lipoid storage diseases often affect the liver as well as other body tissues.[28] In hepatolenticular degeneration (Wilson's disease) pathologic changes are found in the liver and the brain, and aminoaciduria regularly occurs, as well as occasional glycosuria.[29, 30] Present evidence suggests that the liver disease cannot account for the other metabolic abnormalities. Moreover, copper may play an important role. The copper content of the brain at post-mortem examination has been reported to be five to ten times higher in Wilson's disease than in brains from normal subjects, or in 1 case each of obstructive jaundice and multilobular cirrhosis.[31] The urinary excretion of copper is also high in Wilson's disease and is greatly increased by the administration of British Anti-Lewisite (BAL).[32-34] These observations are, at present, difficult to correlate, but are stimulating to thought.

Nutritional Disturbances Resulting from Liver Disease

The effect of established liver disease upon ingestion, digestion, absorption and intermediary metabolism of nutrients is considered in this section, and the evidence for nutritional deficiency occurring as a result of (that is, conditioned by) primary liver disease is evaluated.

Effects of Liver Disease Upon the Ingestion of Food

Anorexia is a frequent symptom of liver disease, and occurs not only in patients with ascites and edema but also in those with acute hepatitis and chronic liver disease without these complications. Anorexia leading to deficient food intake may begin a vicious circle in patients with chronic liver disease by inducing further deficiency, exacerbation of the liver disease and, to complete the circle, more anorexia.

Effect of Liver Disease on Digestion and Absorption of Food

Few extensive and careful studies of digestion and absorption of food have been carried out in patients with severe chronic liver disease. A normal rate of absorption of protein was reported in one study of patients with advanced cirrhosis.[35] Moreover, fecal nitrogen excretion is not increased in patients with liver disease, indicating that digestion and absorption of protein are unimpaired. No defects were found in the absorption of monosaccharides, fat and protein in cirrhosis of the liver, as determined by analysis of blood obtained from collateral abdominal veins, although the studies were not conclusive.[36, 37] One of these studies revealed a higher glucose concentration in the collateral-vein than in the antecubital-vein blood after glucose ingestion, presumably signifying that the portal system was at least one source of the collateral-vein blood. Similar differences were found in 7 of 12 patients with cirrhosis of the liver in another study using fluorescein and thiocyanate as tracers.[38]

The interpretation of blood sugar values after the oral administration of glucose to patients with liver disease is complicated not only by possible abnormalities in absorption but also by altered intermediary metabolism and even by the portal blood bypassing the liver through collateral channels as indicated above. Thus, the great variation in oral glucose tolerance curves from patient to patient is not surprising. Usually, the fasting values are normal, but many patients otherwise have a diabetic type of curve and in some the curve is normal or even flat. To eliminate the factor of absorption, a single intravenous injection of 25 gm. of glucose was given to 25 patients with severe liver disease (mostly chronic cirrhosis) and to 60 normal subjects. No significant difference was found between these two groups.[39] If further experience proves this to be consistently true, the abnormalities following oral glucose administration must relate to abnormal absorption, or to mixing of portal with systemic venous blood. Considering the large volumes of blood that must bypass the liver in severe cirrhosis, this explanation may, indeed, be an important one. However, others have observed a reduced oxidation and glycogenesis from administered glucose by a diseased liver.[40]

The fat-soluble substances, vitamin A and its precursor, carotene, are absorbed poorly in patients with obstructive jaundice due to impaired fat absorption. Impaired absorption of vitamin A after a test dose also occurs in parenchymal liver disease even without jaundice.[41] Impaired dark adaptation in chronic cirrhosis has likewise been noted.[42] Analyses of the vitamin A and carotene contents of human livers have demonstrated that in many illnesses vitamin A is decreased, but the reduction is most

marked in patients with cirrhosis of the liver.[43] Whether the liver deficiency of vitamin A is related to impaired ingestion, digestion and absorption or failure to store vitamin A in the liver is not known. An expected relation has not been found between either vitamin A or carotene levels in plasma and liver and the concentration or distribution of fatty acids in the same locations.[44]

Hypoprothrombinemia occurs regularly in advanced hepatic disease of all varieties and is due mainly to failure of the liver to make prothrombin from its precursors and not to vitamin K deficiency. In a few patients, however, a deficiency of vitamin K may coexist and is then ameliorated by oral, or in the presence of biliary obstruction, parenteral administration of this vitamin. Nevertheless, vitamin K usually cannot raise the lowered prothrombin level in acute or chronic parenchymal hepatic disease.

Effect of Liver Disease on Intermediary Metabolism

The liver has a central role in the intermediary metabolism of many nutrients. Carbohydrate is presented to the liver via the portal system as monosaccharides. The normal human liver appears to metabolize carbohydrate in a manner similar to that of animals.[45] This was demonstrated by hepatic-vein catheterization, and further study indicated that during fasting the normal liver liberates about 3.5 mg. of glucose per kilogram of body weight per minute. Moreover, hepatic retention of glucose followed intravenous glucose administration. The results of hepatic-vein catheterization in patients with various forms of liver disease are awaited with interest. The response of the blood sugar, blood lactic acid and muscle glycogen to intravenous administration of epinephrine has been studied in normal persons, patients with diabetes mellitus and 2 patients with severe acute hepatitis.[46] The latter gave a subnormal hyperglycemic response to the epinephrine although the changes in blood lactic acid and muscle glycogen differed little from those of the normal subjects. African natives suffering from the malignant malnutrition discussed above store administered glucose as liver glycogen poorly.[47] These data, together with those discussed above regarding glucose tolerance, indicate that although the diseased liver may not metabolize carbohydrate normally, present methods do not demonstrate any grave defect.

Galactose and fructose are converted to available glucose or glycogen, probably entirely by the liver. This metabolic function of the liver is independent of the action of insulin. The rate and extent of metabolism of galactose has been used as a sensitive test of liver function.[48, 49]

Food protein reaches the liver as amino acids and perhaps to a small extent as peptides. The amino acids may be synthesized into liver protein, into certain of the plasma proteins, especially albumin, fibrinogen and prothrombin, or, finally, may be deaminized and the glycogenic residues utilized for energy. Some of the amino acids presumably escape immediate deamination or synthesis in the liver, for there is a rise in the systemic venous amino acid concentration for approximately an hour after a protein meal. Whether the source of protein for the tissues is chiefly the plasma protein produced by the liver from absorbed amino acids[50] or rather is from amino acids passing through or released by the liver is not known. Whichever the source, the body is able to utilize amino acids administered by vein for tissue protein synthesis even in the face of severe liver disease.[51] This does not mean that the intermediary metabolism of each of the amino acids is normal in liver disease — in fact, abnormalities in the metabolism of glycine, tyrosine and methionine have been described.[52-54] Nevertheless, these abnormalities, as far as we know, do not significantly influence protein nutrition in liver disease. Thus, a patient with severe liver disease is able to digest protein and absorb amino acids and utilize them for the building of body tissue, including new liver tissue. A positive nitrogen balance occurs even in the face of severe liver disease when there is a need for body protein repletion, if sufficient calories are available so that protein or amino acids are not used for energy.

Some patients with liver disease excrete certain amino acids in the urine in amounts slightly increased above normal, but these losses are nutritionally unimportant.[55, 56] Furthermore, the urinary excretion pattern of essential amino acids in patients with hepatic disease is similar to that observed in normal persons. Patients with acute yellow atrophy of the liver present exceptions to this, however, since the amino acid content of the blood and urine is abnormally high. This is attributed to an excess production of amino acids from the rapid autolysis of liver tissue and to decreased deamination of amino acids by the necrotic liver. The detection of tyrosine and leucine crystals in the urine of patients with acute yellow atrophy and other types of severe liver disease has been used as a test for impairment of liver function, but the urinary loss of these amino acids is likewise not nutritionally important.

Acute and chronic liver disease is regularly associated with hypoalbuminemia, which may be marked. This reduced serum albumin concentration probably results from inability of the diseased liver to produce albumin at a normal rate, since the liver is the site of albumin synthesis. A reduced rate of incorporation of radioactive sulfur into plasma proteins substantiates this.[57] Furthermore, patients with chronic cirrhosis metabolize intravenously injected normal human serum albumin at a rate comparable to that observed in normal subjects.[58] Continued and often significant losses of protein into the ascitic fluid and its subsequent removal by repeated paracentesis contribute to the

hypoalbuminemia. The removal of 10 liters of ascitic fluid, for example, may entail a loss of 100 gm. of protein to the body. The reduction in serum albumin is usually associated with a rise in the serum globulin concentration, especially the gamma globulin, although sometimes the beta and alpha fractions are increased as well (electrophoretic analysis).[59, 60]

Little is known of abnormalities in intermediary fat metabolism due to disease of the liver. Fat is transported in the blood, in part at least, as phospholipid (mostly choline containing) and as esters of cholesterol, which are produced mainly by the liver. Determinations of the serum lipids in patients with primary liver disease have failed to reveal striking or consistent abnormalities except that the blood content of cholesterol esters and of phospholipid is low, occasionally markedly so.[44, 61] A consistent relation between blood and liver lipids has not been established in man. Further study of fat metabolism in fatty liver disease and cirrhosis in man is indicated.

The water-soluble vitamins are generally assumed to be rapidly absorbed and transported to the liver via portal radicles. Many of the vitamins of the B complex must be phosphorylated, presumably in the liver, before they become active coenzymes. Low blood concentrations of diphosphothiamine (cocarboxylase), which are probably due to impaired phosphorylation of thiamin, have been observed in patients with chronic cirrhosis.[62] A deficiency of diphosphothiamine may account for the increased pyruvate concentration of the blood in cirrhosis just as thiamine (and hence diphosphothiamine) deficiency does in beriberi.

The existence of a chronic, moderately severe, usually macrocytic, sometimes normocytic anemia in liver disease is well established.[63] However, the anemia does not respond to the administration of liver extract with reticulocytosis or other evidences of hematopoiesis unless pernicious anemia or nutritional macrocytic anemia coexists. Some immaturity in red-cell formation is apparent in the bone marrow in cirrhosis, but megaloblasts characteristic of pernicious anemia are not usually evident, although a recent report cites 3 cases with megaloblastic proliferation.[64] Leukopenia and thrombocytopenia may be seen in conjunction with the anemia, as in other diseases complicated by portal hypertension. The recent discovery of vitamin B_{12} as an active factor in the treatment of many macrocytic anemias suggests deficiency of this vitamin in the etiology of the anemia of liver disease. At present there is no evidence that this is so, particularly since large doses of liver extract that contain therapeutic quantities of vitamin B_{12} are not effective in increasing blood production in liver disease. Similar considerations may apply to the animal protein factor,[65] which is either identical with or similar to vitamin B_{12}. If chronic blood loss occurs in patients with liver disease, iron-deficiency and hypochromic anemia result, as in any patient with blood loss.

Scurvy occasionally occurs in patients with cirrhosis, particularly chronic alcoholic patients, and can usually be attributed to a deficient intake of ascorbic acid. Moreover, patients with chronic cirrhosis, although not clinically scorbutic, frequently have low blood levels of ascorbic acid. Impaired storage or metabolism of vitamin C may exist in liver disease, but little research has been done on the problem. Many patients with cirrhosis have a bleeding tendency, characterized sometimes by bleeding gums, often by purpura and occasionally by gastrointestinal bleeding. Apart from local factors this may be related to a deficiency of blood prothrombin, of platelets or of fibrinogen. In many cases, however, inadequate hemostasis in liver disease remains unexplained. Yet there is no evidence that an abnormality of vitamin C metabolism accounts for the abnormal bleeding tendency or the appearance of purpura.

It is clear that data are meager concerning the intermediary metabolism of the vitamins in liver disease. Clarification awaits the further development of specific and convenient biochemical methods for the determination of many of these substances. The common assumption that such clinical conditions as cheilosis, angular stomatitis, glossitis and corneal injection are necessarily signs of specific vitamin deficiency has led to confusion. These lesions may arise from local conditions and from other disturbances in nutrition, possibly including amino acid and protein deficiency. Moreover, these signs are not particularly common in patients with chronic liver disease.

Certain alterations of the electrolytes, sodium and chloride and of water in patients with liver disease deserve comment. Whatever the ultimate cause or causes of ascites may be, patients with chronic liver disease repeatedly forming ascites characteristically excrete only small amounts of urinary sodium, as little as 1 to 5 milliequiv. daily,[66, 67] regardless of sodium intake. The factors responsible for the failure to excrete urinary sodium are not known, although increased antidiuretic activity attributable to hormones elaborated by the posterior pituitary body or, more particularly, by the adrenal glands, or by both, may be responsible and due, it is suggested, to failure of the diseased liver to metabolize certain hormones normally.[68]

Iron in plasma is bound to a specific metal-binding globulin, which in normal persons is saturated to about a third of capacity with iron.[69] The iron-binding capacity, a measure of the metal-binding globulin, is reduced slightly in chronic liver disease, from about 300 to between 200 and 250 microgm. per 100 cc. The total iron content of plasma is essentially normal (about 100 microgm.

per 100 cc.) or only slightly low, so the metal-binding protein is more saturated with iron than usual. Hemochromatosis is the only disease in which very high levels of serum iron occur. Values of 200 or even 300 microgm. per 100 cc. are usual, and the metal-binding protein is 85 to 100 per cent saturated with iron. Except in hemochromatosis there is no evidence of a disturbance of iron metabolism in liver disease, although, as noted above, the relation of hemochromatosis to nonpigment cirrhosis may not be as absolute as heretofore believed.

The metabolism of copper in human cirrhosis has been little studied although it may play an important role in Wilson's hepatolenticular degeneration, as discussed above.

Nutrition in the Therapy of Liver Disease

The provision of a nutritious diet is the cardinal principle in the feeding of patients with most illnesses. To encourage the patient to eat the food provided is equally important. Patients with liver disease are no exception to these dicta and receive optimal nutritional therapy, as far as now known, if these two basic principles are followed with enthusiasm, care and common sense. Alteration of the kind or quantity of dietary constituents is necessary in certain circumstances described below. When such alterations are necessary, adherence, as far as possible, to a well balanced diet composed of natural foods provides the most effective nutritional therapy.

Most patients with chronic liver disease show wasting of body tissues because of a combined deficiency of calories and protein attributable to inadequate intake and anorexia, rather than to defects in intermediary metabolism. As noted above, these patients maintain positive calorie and protein balances if they consume nutritious foods in sufficient quantity. Thus, to correct these deficiencies the diet must provide calories and protein in quantities larger than those needed for maintenance of normal persons. The food intake is often increased by food supplements such as eggnogs, enriched if necessary with whole-protein preparations. Such supplements must be attractive, and the patient must be encouraged to consume them and convinced that they offer specific therapy. The addition of purified vitamin preparations to such a diet is unnecessary[70] since the nutritious diet will provide optimum allowances of the vitamins in a suitable mixture of nutrients. This is true even if lesions suggesting specific vitamin deficiencies are seen.

The wasting regularly seen in chronic liver disease, together with the frequent occurrence of testicular atrophy, loss of hair and feminizing traits, suggests a deficiency of testosterone. Some clinical improvement has been observed after the administration of this hormone to patients with cirrhosis of the liver. However, nitrogen-balance studies indicate that its anabolic effect is not great and may be reversed when administration is discontinued. More important, increasing the dietary protein intake induces a greater protein anabolic effect more easily and economically than the administration of testosterone.[71]

As previously discussed, conclusive evidence is lacking that deficiency of lipotropic substances is a cause of human liver disease. Phospholipid formation was increased in 7 patients with cirrhosis after single large doses of choline or methionine, suggesting that a deficiency of lipotropic substances existed.[72] Nevertheless, the rate of phospholipid formation was not significantly lower in the patients than that observed in normal persons, nor were differences observed after prolonged treatment of the patients with choline.[73] Moreover, there is no statistically valid clinical evidence that the addition of choline or methionine to a nutritious diet induces a more rapid, more complete or more certain recovery than the diet alone.[74]

Although a protein-saving (anabolic) effect has been observed in patients with chronic liver disease after supplementation of a high-protein, high-vitamin diet with choline and methionine,[75] other studies indicate that these nutrients induced a nitrogen balance no more positive than could be accounted for by retention of the nitrogen contained in the administered agents. Moreover, increases in dietary protein intake were regularly accompanied by increases in positive nitrogen balance.[71]

It may be concluded that data are lacking to indicate that lipotropic substances are etiologically important or therapeutically useful in liver disease in man. However, the evidence, especially from animal studies, implies that the therapeutic diet should provide these as well as other nutrients in optimum amounts.

Optimum quantities of nutrients are probably best provided as they naturally occur in foods. A nutritious diet used in this clinic providing 100 gm. of protein daily furnishes approximately 2.8 gm. of methionine and 0.9 gm. of choline (Table 1). The requirements of patients with liver disease for these substances are unknown, as is the requirement of normal persons for choline. The daily requirement of normal subjects for methionine is stated to be 1.1 gm. and the recommended allowance 2.2 gm.[83] Presumably, some of the methionine in the food is used in the body for choline synthesis. Because of the paucity of knowledge it is recommended that these nutrients be supplied in foods, as shown in Table 1, rather than as pure substances. Supplements of methionine may even be harmful.[54]

Reduction in dietary fat consumption is usually indicated for patients with deep jaundice and a marked decrease or absence of bile in the gastrointestinal tract, as in the early stages of infectious

hepatitis, to reduce indigestion and fatty diarrhea, which are sometimes distressing symptoms. Adequate calorie intake is maintained by an increase in the proportions of carbohydrate and protein. As this situation is usually of short duration, the fat-soluble vitamins need not be provided except for vitamin K, which should be given intramuscularly as one of the synthetic water-soluble preparations in amounts approximating 5 mg. daily. Appearance of a reasonable amount of bile in the gastrointestinal tract, observed by darkening of the stool color, permits an increase in dietary fat to tolerance. No reduction of dietary fat is necessary in chronic parenchymal liver disease, except, as noted, when communities, are available.[77, 85, 86] Signs of sodium deficiency are rarely seen even though the strict low-salt diet is continued for many months.

Specific feeding measures may be indicated in gastrointestinal bleeding when bleeding has ceased. Complicating gastrointestinal hemorrhage in patients with chronic hepatic disease usually originates from peptic ulcer, which occurs commonly in such patients, or from varices in the esophagus or cardia of the stomach. Prevention of recurrence of active bleeding may be aided in either circumstance by the use of the usual ulcer regime, with particular emphasis on small feedings of milk and cream or

TABLE 1. *A Nutritious Diet Low in Sodium.**

FOOD ITEM	QUANTITY	APPROXIMATE NUTRIENT CONTENT			
		PROTEIN	SODIUM	CHOLINE	METHIONINE
	gm. or cc.	*gm.*‡	*mg.*§	*gm.*¶	*gm.*‖
Low-sodium milk powder†	100	27.0	10.0	0.08	0.76
Cream, light	30	0.8	15.6	?	?
Egg	50	6.4	70.0	0.37	0.21
Cereal (cream of wheat)	20	3.0	0.4	?	?
Bread (low sodium)	200	16.0	4.0	0.25	0.40
Butter (sweet)	50	0.2	2.5	0.01	0.0
Jelly	60	0.0	4.2	?	?
Meat (beef)	120	32.2	63.6	0.09	1.03
Meat (chicken)	60	15.8	47.0	0.05	0.34
Potato	200	4.0	1.2	0.01	0.05
Peas	50	1.6	0.4	0.02	0.01
Carrots	50	0.6	14.5	0.01	TR
Orange juice	100	0.0	0.2	0.01	0.00
Apple	200	0.6	0.2	0.01	0.00
Strawberries	150	1.2	1.2	0.01	0.00
Sugar	100	0.0	0.0	0.00	0.00
Coffee or tea	*ad lib.*	0.0	0.0	?	0.00
Totals		109.4	235.0	0.92	2.80

*This diet, which provides approximately 3000 calories and 115 gm. of fat, is rigidly restricted in sodium content, and suitable for patients with ascites and edema. Use of special low-sodium foods is unnecessary for patients with liver disease without these complications.

†"Lonalac," supplied by Mead Johnson Co., Evansville, Indiana.

‡Data of Bowes and Church.[78]

§Data of Bills et al.[77]

¶Average values derived from Borglin,[78] Wohl,[79] and Block and Bolling.[80]

‖Data of Stokes et al.[81] and Millares and Fellers.[82]

high-grade biliary obstruction coexists. Moreover, since low-fat diets are usually unappetizing, adequate fat, comprising part of a nutritious diet, should be provided for most patients with liver disease.

The three most important complications of chronic liver disease are ascites and edema; bleeding esophageal varices or bleeding peptic ulcer; and liver coma. Each may require specific alteration in the kind of food provided or the method of its administration.

The accumulation of ascites and edema may be remarkably well controlled by provision of a diet rigidly restricted in sodium.[67, 84] Cessation of ascitic-fluid formation saves protein and nitrogen for the patient since loss by paracentesis is alleviated. The low-sodium diet must provide the other nutrients in sufficient quantities (Table 1). Several cookbooks and tables useful for assembling such diets and calculating their salt content, including the sodium content of the drinking water in some protein-enriched milk mixtures at frequent and stated intervals throughout the day.

The pathogenesis of liver coma is not known, but there is no evidence that the metabolism of essential and nonessential nutrients is significantly altered by the onset of coma.[87, 88] Therefore, an attempt should be made to support the patient's nutrition, especially since hepatic coma is not inevitably an irreversible state. Since a stuporous or comatose patient cannot eat, either tube or parenteral feeding is required. This is true not only of patients with hepatic coma but also of those with liver disease in whom anorexia makes the usual oral feeding impossible or not sufficient in quantity to provide the nutrients required.

As a rule, tube feeding may be accomplished without much difficulty in patients with acute and chronic liver disease. In our experience bleeding from varices or from peptic ulcer induced by intubation occurs rarely so that tube feeding, if necessary, may be instituted in spite of such a diag-

nosis. Needless to say, in the presence of gross upper gastrointestinal bleeding from any cause, intubation for feeding is contraindicated. Natural foods should be used in the preparation of mixtures for tube feeding. Whole milk supplemented with other natural foods forms the basis for most intubation diets. A sample formula for an intubation diet is shown in Table 2. There is no advantage to providing hydrolyzed protein since digestion and absorption proceed without obvious difficulty.

Protein as a hydrolysate can be given intravenously in adequate amounts, but it is difficult to fulfill the caloric requirement with parenterally administered glucose. Fat preparations suitable for intravenous use will be of great help in providing sufficient calories in intravenous feeding if they are shown to be well tolerated in liver disease.[89] It was noted above that patients with liver disease handle intravenous injection of glucose and protein hydrolysates in a manner differing little from normal. Liver disease does not significantly decrease the usefulness of these materials given as nutrients by this route. From 50 to 100 gm. of hydrolyzed protein may be given daily, the amount depending upon body weight (at least 1 gm. per kilogram is recommended). Positive nitrogen balance can be achieved even when adequate quantities of such hydrolysates are given as the sole source of nitrogen, provided sufficient calories are simultaneously included. Vitamin administration is required with intravenous feeding. A mixture of ascorbic acid, thiamine, riboflavin, niacin and vitamin K may be administered parenterally. In addition to the purified preparations, a cruder source of the vitamin B complex may be given in the form of liver extract, either intramuscularly or in larger amounts intravenously if preparations specifically prepared for the latter route of administration are used. Recent studies report that patients with hepatic cirrhosis live longer and have fewer complications when given large amounts (up to 120 cc. weekly) of liver extract intravenously in addition to a nutritious diet.[90, 91] These results although interesting and suggestive, require confirmation because of the wide variability in remission and relapse in patients with liver disease.

The optimum mixture and distribution of nutrients found in a nutritious diet composed of natural foodstuffs cannot be expected when feeding must be done parenterally with purified or synthetic materials. Nevertheless, the nutrients now believed to be essential can be provided without difficulty. One hundred grams of protein as a protein hydrolysate contains 2 or 3 gm. of methionine, which will provide for the synthesis of choline. Choline is rarely administered intravenously because of the very slow speed of administration required on account of its powerful vasodilating effect.

The intravenous administration of normal human serum albumin artificially to raise the frequently reduced serum albumin concentration in patients with chronic liver disease has not succeeded well as a diuretic.[92-94] Albumin given intravenously to man remains intact for several days and so is only slowly available for tissue nourishment, in contrast to protein hydrolysates, which are immediately available.[58, 95] This product is also expensive and difficult to obtain. Adequate quantities of protein as serum albumin intravenously may raise the albumin concentration and the plasma volume sufficiently to invite danger from pulmonary edema and gastrointestinal bleeding. Evidence of

TABLE 2. *Formula for Tube Feeding.**

Food Item	Quantity	Protein	Carbohydrate	Fat	Calories
		gm.	gm.	gm.	
Milk, whole, homogenized (1 quart)	975 cc.	33	48	38	666
Liver, raw, ground	100 gm.	20	6	3	132
Cream, 20 per cent	100 cc.	3	4	20	208
Egg (1)	50 gm.	6	0	6	79
Skim-milk powder	40 gm.	14	21	0	144
Sugar or "Dexin"	200 gm.	0	200	0	800
Orange juice†	150 cc.	0	15	0	60
Totals	1,500 cc.‡	76	294	67	2,089

*The nutrient composition is calculated from Bowes and Church.[78]

The protein and caloric content of the formula can be adjusted to the individual need by increasing the volume or frequency of feedings, or both. For example, feeding of 150 cc. of this formula each hour or 75 cc. each half hour from 7 a.m. to 9 p.m. provides a total fluid volume of 2250 cc. containing 118 gm. of protein and 3134 calories.

A tube-feeding schedule is best started by providing only whole milk in small quantity (25 to 50 cc.) every ½ to 1 hr., especially in patients who have not been eating. The formula can then be increased in concentration and in volume of each feeding as tolerated by the patient, until an adequate food intake is achieved.

Attention to the following contributes to the success of intubation feeding: refrigeration of the mixture but allowing the portion to be fed to warm to room temperature before administration; allowing each feeding to flow slowly into the tube; and thoroughly rinsing the tube with 50 to 100 cc. of water after each feeding. The latter also increases the fluid intake. If electrolytes are required, appropriate electrolyte solutions can be used for this purpose. Solutions containing sodium should not ordinarily be used in patients with ascites and edema.

†Orange juice is not mixed with the other ingredients of the formula, but is given separately. Ascorbic acid, 100 mg. daily, may be given in place of orange juice, if necessary.

‡Approximate total fluid volume. The total food intake (1500 cc.) can thus be provided by the feeding of 100 cc. of formula each hour from 7 a.m. to 9 p.m.

the importance of these complications, especially in patients with esophageal varices, has recently been presented.[94] Nevertheless, patients with infectious hepatitis may achieve some benefit from intravenous administration of albumin.[96]

Although consumption of nutritious foods is one of the most important therapeutic measures in liver disease, other factors must not be forgotten. Rest is important,[97] and abstinence from alcohol, at least when previously used to excess, is imperative. Clinical and histologic improvement was observed in patients with Laënnec's cirrhosis during a control period of bed rest and alcohol withdrawal during which only a minimal diet was provided.[98] Rapid and marked improvement, as observed clinically and by laboratory tests of liver function, occurred in other patients with fatty livers who ingested calorically adequate diets devoid of protein.[99] Morphologic improvement, as determined by serial liver biopsies, did not occur in the latter patients, however, until a nutritious diet adequate in protein was provided. Results such as these illustrate the difficulty in the evaluation of specific nutrients in the pathogenesis and therapy of liver disease in man. Consumption of a "nutritious diet" remains the best method of supplying nutrients, and is an important therapeutic measure in patients with liver disease.[100]

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36461

PRESENTATION OF CASE

A sixty-five-year-old woman was admitted to the hospital because of repeated episodes of disorientation and bizarre behavior.

Four years prior to admission the patient fell and cut her forehead, but did not lose consciousness. Two weeks later she had a brief episode of coma, which was followed by episodic disorientation lasting two weeks. She was studied at another hospital and told she had hypertension. About this time she began to have dyspnea on climbing one flight of stairs, orthopnea requiring three pillows for relief and nocturia (three times). Her physician treated her with digitalis and a low-salt diet, and she was able to carry on with her usual activities. Three days before admission, while engaged in routine housework, she suddenly became dizzy and fell to the floor, without losing consciousness. During the next three days she had ataxia, was unable to write and complained of insomnia and nervousness. There was a slight increase in her usual mild cough but no chest pain, hemoptysis or leg pain.

There was no history suggestive of rheumatic fever or previous cardiac complaints. A gradual 35-pound weight loss had occurred over the past four years. Both parents had died of cerebral hemorrhage, her father at the age of sixty-two and her mother at the age of seventy-eight.

Physical examination revealed a moderately disoriented, poorly nourished, slightly cyanotic woman in no acute distress. A Grade III hypertensive retinopathy was noted. The neck veins were flat, and there was no edema. There were rales at the left-lung base posteriorly, whereas the right base was dull to the level of the ninth thoracic vertebra. The point of maximum impulse was felt in the anterior axillary line in the sixth intercostal space. The heart sounds were tumultuous, with a loud third sound. The pulmonic second sound was louder than the aortic. A harsh systolic murmur was heard over the entire precordium, and a low-pitched, apical, mid-diastolic murmur was also heard by some observers. A pulse deficit was noted. The liver was percussed three fingerbreadths below the costal margin. Except for a clouded sensorium, neurologic examination was negative.

The temperature was 100°F., the pulse grossly irregular at 80, and the respirations 20. The blood pressure was 170 systolic, 110 diastolic.

The urine had a specific gravity of 1.022 and gave a ++ test for albumin; the sediment contained 5 red cells, 20 white cells and many bacteria per high-power field. Examination of the blood disclosed a hemoglobin of 15.1 gm. and a white-cell count of 11,300, with 80 per cent neutrophils. The sodium was 139.8 milliequiv., the potassium 5.2 milliequiv., the chloride 95 milliequiv., and the carbon dioxide 31.6 milliequiv. per liter, and the phosphorus 3.1 mg., the calcium 10.2 mg., the nonprotein nitrogen 23 mg., the fasting blood sugar 141 mg., and the cholesterol 184 mg. per 100 cc. The prothrombin time was 70 per cent of normal.

FIGURE 1.

A roentgenogram of the chest showed patchy density at the left-lung base and fluid in both costophrenic sinuses, more marked on the left. Vascular markings were accentuated in the remaining lung fields. There was marked cardiac enlargement, which appeared to involve all chambers (Fig. 1).

The aorta was tortuous, and there was a soft-tissue prominence in the right anterior and superior mediastinum. An electrocardiogram was consistent with left ventricular hypertrophy, early left-bundle-branch block and well controlled auricular fibrillation at an average ventricular rate of 55 to 60.

The patient was placed on a low-salt diet, 0.1 mg. of digitoxin per day and 15 mg. of phenobarbital three times a day. During the first five days the temperature remained between 100 and 101°F. Cheyne–Stokes respiration, with 20-second to 30-second periods of apnea, began on the third day, but there was slight improvement in the mental status. On the fifth day the patient was found covered with sweat and complaining of coldness and numbness of the right hand and arm. Although the blood pressure was 230 systolic, 130 diastolic, no radial pulse could be felt on the right. An embolectomy was performed at once under local anesthesia, with removal of a firm, 3-cm. thrombus from the right brachial artery. Two-hundred milligrams of heparin was injected directly into the artery at the close of the operation, and 200 mg. of Dicumarol was given by mouth. There was immediate return of circulation to the arm, but during the course of the night there was oozing from the wound, with an estimated blood loss of 200 to 300 cc. The clotting time forty-five minutes after the intra-arterial injection of heparin was over 5 hours, declining to 55 minutes on the following day. The prothrombin time was 26 per cent of normal. No further anticoagulants were administered.

About twenty-four hours after the operation the temperature rose sharply to 105°F., the patient sank into a deep coma, and a left Babinski sign and left flaccid paresis appeared. On the following day the respirations rose to 40 per minute, and signs of consolidation appeared at the left base. Coarse rales were heard throughout the chest, and the trachea filled repeatedly with mucus, requiring suction. The neck veins were slightly distended, and the pulse was irregular at a rate of 78. The patient was given 100,000 units of penicillin and then placed on 300,000 units of Crysticillin a day. The temperature, however, continued to rise, reaching a high of 106°F., and the respirations increased to 50 per minute. A lumbar puncture performed on the third postoperative day yielded grossly bloody xanthochromic spinal fluid under an initial pressure equivalent to 180 mm. of water that contained 24,000 red cells, 4 polymorphonuclear leukocytes and 2 lymphocytes per cubic millimeter. The patient died quietly on the fourth postoperative day.

Differential Diagnosis

Dr. Allen G. Brailey*: It seems certain that this woman died as the result of cerebrovascular disease, and it is up to me to discuss the possible nature and origin of the vascular accidents reported. She had had episodes of disturbance of cerebral function of one sort or another for a total period of four years. For the most part, at least, these came on suddenly rather than gradually, and over a succeeding period of days or weeks the symptoms gradually improved. This sequence of sudden onset with maximum symptoms that tend to improve somewhat with lapse of time is characteristic of vascular occlusions. Were these occlusions due primarily to thrombosis or to embolism, or can they have been related to the fall that she is said to have had two weeks before the first episode of coma and disorientation? It is impossible to gauge the severity of this injury. She cut her forehead. She was not made unconscious, but relatively minor blows on the head in elderly people may result in serious damage and precipitate the clinical syndrome of chronic subdural hematoma. This woman's injury does not appear to have resulted in a subdural hemorrhage, but it is conceivable that it produced enough tissue damage to precipitate a subsequent thrombosis that ushered in the first attack of coma and disorientation.

However, I do not have to fall back upon such a fanciful cause for cerebral thrombosis. She was an elderly woman with marked hypertension, both of whose parents died of cerebrovascular accidents. Almost certainly, she had widespread atherosclerosis, a condition in which so-called spontaneous cerebral thromboses are very common. Often, there are very numerous occlusions of minor vessels with transient neurologic symptoms only if the resulting infarcts are large enough, but with steadily diminishing mental function to attest to the widespread encephalomalacia. There is a rather nebulous and ill defined clinical state seen in some patients with severe hypertension that is called hypertensive encephalopathy. I wonder if someone did not suggest that this woman with a Grade III retinopathy, marked and variable hypertension and bizarre cerebral symptoms had hypertensive encephalopathy. The hypertensive crises supposed to characterize this state are hard to explain, but the cerebral symptoms are quite surely due to the successive occlusion of many minor arterial twigs. I think one has to mention here the possibility of polyarteritis nodosa. There is certainly little in favor of it, but she did have blood cells in the urine and peripheral thromboses could have been easily overlooked. Certainly, she had adequate mechanism for the development of thromboses, but she had an even better basis for chronic or recurrent embolism — namely, fibrillating auricles. Perhaps it would be well to leave the vascular problems for a moment to give a little thought to the heart.

May I see the x-ray films now?

Dr. James J. McCort: The x-ray films of the chest show a very large heart (Fig. 1). On the right side a double contour is seen, the carina is widened,

*Assistant physician, Massachusetts General Hospital.

and the left main bronchus is pushed upward and posteriorly by the enlarged heart. These three signs indicate marked enlargement of the left auricle. There is also prominence of the heart to the left and posteriorly in the apical region, which suggests some enlargement of the left ventricle. The slight bulge at the heart anteriorly may indicate slight enlargement of the right ventricle. The pulmonary vessels are dilated and prominent. Fluid is present in both bases, more marked on the left side, and for this reason I am unable to outline the left leaf of the diaphragm. There is some increase in density in the left base that makes one wonder about infarction. The widening of the superior mediastinum described in the protocol seems to be due to engorgement of the vessels, probably the superior vena cava and innominate veins.

DR. BRAILEY: Is not the outline of the heart more in favor of rheumatic rather than hypertensive heart disease? It has a prominence in the region of the left auricle.

DR. MCCORT: The left auricular enlargement favors disease in the region of the mitral valve.

DR. BRAILEY: You do not think she had a tumor in the superior mediastinum or perhaps an intrathoracic goiter?

DR. MCCORT: I cannot rule out either possibility without fluoroscopy. From the films I think this is more likely to have been vascular engorgement.

DR. BRAILEY: What kind of heart disease did she have? Was it hypertensive and arteriosclerotic, or was it rheumatic heart disease with mitral stenosis? There was no history of rheumatism, but that need not discourage me. Auricular fibrillation may occur in almost all forms of heart disease, but it is a very common late development in rheumatic heart disease. At the age of sixty-five rheumatic heart disease is much less frequent than hypertensive, but it does occur, of course. Dr. Edward F. Bland has reminded me that Dr. Samuel A. Levine believes that hypertension may tend to prolong the life of the person with mitral stenosis. It is said that some observers heard a mid-diastolic rumble — the characteristic murmur of mitral stenosis. This seems fairly weighty evidence. One positive observation is worth several negative ones. The configuration of the heart is very suggestive of mitral stenosis, and finally a loud third heart sound was heard, an accentuation of ominous significance often heard in mitral stenosis and also in failing hearts. I think she had rheumatic heart disease with mitral stenosis. Almost certainly, she had some coronary-artery disease as well, but it is unlikely to have contributed much to her clinical state. The question arises what relation, if any, the hypertension had to the heart disease. If emboli had repeatedly lodged in the kidneys, their function might have been so reduced that a compensatory hypertension developed. However, the kidney function appears to have been surprisingly good, and presumably the hypertension was of the usual essential variety.

She did have at least one embolus, for one was removed from the right brachial artery. Cerebral embolism is very common even when no source can be found. In this case it is a safe bet that many, at least, of the cerebral insults were due to embolism from the left auricle. The final episode was characterized by hypothermia, tachypnea and deepening coma. A spinal puncture revealed increased pressure and a grossly bloody spinal fluid. Obviously, she had had a massive hemorrhage into or about the third ventricle. This may have been the inevitable result of the hypertension and weakened arteries, but one wonders what role anticoagulant therapy played in its development.

Finally, I think I ought to note the gradual weight loss of 35 pounds. There was a mass in the superior mediastinum, which I have ignored thus far. The fasting blood sugar was high. Could she have had thyrotoxicosis as an added difficulty and a further reason for auricular fibrillation? I do not know how to be sure that she did not, but I think she had trouble enough without it. Presumably, the mental and circulatory states offer an adequate explanation for the loss of weight.

DR. JACOB LERMAN: I should like to ask Dr. Brailey to comment about the harsh systolic murmur.

DR. BRAILEY: Nothing was said about it after she was admitted to the hospital. I should think it might have been a regurgitant murmur due to dilatation. It might have been an aortic murmur as the result of relative aortic stenosis.

DR. LERMAN: At her age, I should say it was calcareous disease of the aorta.

DR. EDWIN O. WHEELER: By the time I saw the patient on the day after entry, I was unable to hear any systolic murmur. She had a short, rough, mid-diastolic rumble at the apex but had no systolic murmur. Before that I think it was described as loud.

DR. BRAILEY: I think this patient had rheumatic heart disease with mitral stenosis, cerebral arterial embolism and thromboses essentially, and finally cerebral hemorrhage and pneumonia.

CLINICAL DIAGNOSES

Cerebral hemorrhage.
Essential hypertension.
Rheumatic heart disease.
Embolectomy, right brachial artery.

DR. BRAILEY'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis.
Cerebral arterial embolism and thromboses.
Essential hypertension.
Cerebral hemorrhage (terminal).
Pneumonia (terminal).

Anatomical Diagnoses

Cerebral hemorrhage, massive, right.
Rheumatic heart disease, active.
Hypertensive heart disease.
Coronary-artery disease.
Infarcts, old, kidneys and spleen.
Bronchopneumonia.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed that the immediate cause of death was a massive cerebral hemorrhage involving the right side of the brain. Unfortunately, the hemorrhage had filled so much of the hemisphere that we were unable to find any evidence of the old disease that she almost certainly had. More likely they were thrombi rather than emboli, with subsequent infarction.

The heart was enlarged, weighing over 600 gm., and showed very marked enlargement of the left auricle that was due to mitral stenosis. The chordae tendineae were thickened and granular. In addition, we saw little verrucae, some of which extended down along the chordae tendineae, which I thought was consistent with active rheumatic infection or at least subacute rheumatic infection. The aortic valve showed similar verrucae and slight interadherence of two cusps — very slight aortic stenosis. I do not believe the harsh systolic murmur was due to that degree of stenosis. The microscopical sections of these nodules show some palisading and, I think, are quite consistent with low-grade, smoldering rheumatic infection. To confirm this we did find in the myocardium a few suggestive Aschoff bodies. In addition there was a great deal of scarring due to coronary-artery disease, which this patient had as well. The fact that the right ventricular wall was not hypertrophied shows that the left auricle probably was able to compensate enough to prevent a pulmonary hypertension as a result of the mitral disease. At least, we were unable to find anything in the lungs that would fit in with a true decompensating mitral valve. I believe the size of the heart was due to the combination of rheumatic involvement and hypertension. We were unable to find the source of the embolus to the brachial artery, but we thought it must have come from the left auricle because there were also old infarcts of the kidneys and spleen. At the time of autopsy, no thrombi were found in the left auricle. Terminally, she did have a bronchopneumonia.

CASE 36462

Presentation of Case

A thirty-two-year-old woman was admitted to the hospital because of pain and swelling of the right upper arm.

Two months before entry, without antecedent illness or trauma, the patient developed low-back pain, coccydynia and right-thigh discomfort. She was treated by her physician with strapping and Sitz baths. The pain was subsiding under this regime when she developed pain in the right shoulder. This was diagnosed as bursitis and was treated by exercise, diathermy and Anacin. Pain persisted in spite of this, and a local anesthetic was injected into the shoulder, with some relief of symptoms. Three weeks before admission the patient's arm began to swell. She was placed on penicillin (dosage unknown), but the upper arm became progressively more swollen, tense, red and extremely painful. She also complained of right axillary pain and was told that the axillary lymph nodes were infected. For twelve days penicillin therapy was maintained, without clinical improvement. Forty-eight hours before entry x-ray examination revealed a destructive lesion of the upper humerus.

Twenty years before admission following trauma the patient developed osteomyelitis of the left upper femur for which, during the following ten years, repeated incisions, drainages and sequestrectomies were performed. Eight years prior to admission a saucerization of the left femur was done, with much improvement, and the patient had only occasional pain in the area during the next two years. Following this interval, however, pain and tenderness recurred for which daily penicillin injections were given, with no recurrence of symptoms referable to the thigh. An appendectomy had been performed some years before.

The patient's father had died of pneumonia. Her mother had died of carcinoma of the breast. One sibling had diabetes. There was no family history of intimate association with tuberculosis.

On physical examination the lungs were clear. The heart was not enlarged, the rhythm was regular, and there were no murmurs or thrills. The abdomen showed a well healed right McBurney scar and was otherwise normal. Several well healed scars were noted on the medial aspect of the left thigh. The right upper arm was swollen. The overlying tissue was tense. Acute tenderness was elicited on touching the upper outer aspect. The extremity was held relatively immobile because of pain on movement. The right axilla was full, the swelling being most marked in the axillary folds. No enlarged axillary lymph nodes were palpable. A small, bean-sized freely movable, nontender, right superficial supraclavicular lymph node was palpated.

The temperature was 98°F., the pulse 90, and the respirations 20. The blood pressure was 100 systolic, 60 diastolic.

The urine was normal. Examination of the blood showed a hemoglobin of 13.4 gm. per 100 cc. and white-cell counts of 8300 and 9000. The serum calcium was 9.5 mg., the phosphorus 3.4 mg., and the phosphatase 1.4 units per 100 cc. The sedimentation rate was 60 mm. per hour. X-ray examination of the chest was negative. Films of the humerus disclosed an extensive patchy destruction of the

upper and middle thirds of the bone and a small area of periosteal reaction in the upper inner aspect (Fig. 1). There appeared to be a diffuse tissue swelling about the right upper arm, suggesting edema rather than a sharply defined mass. There was a deformity of the lesser trochanter of the

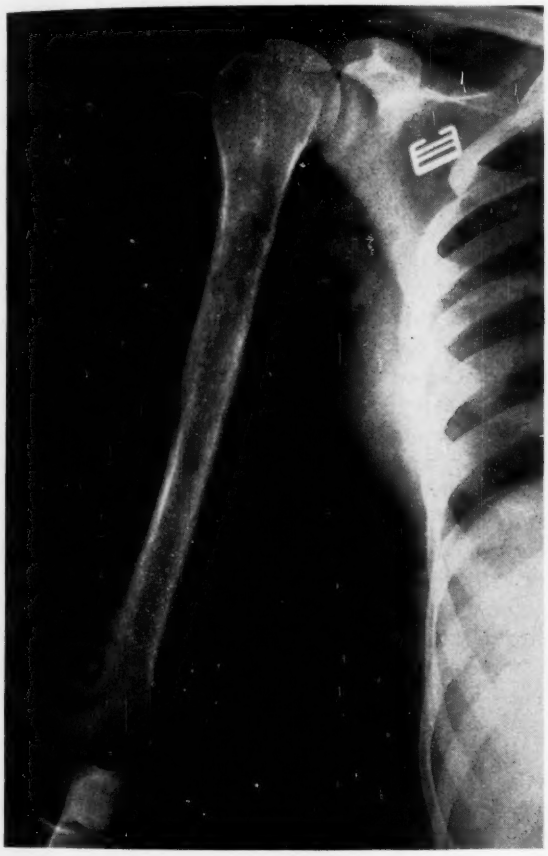

FIGURE 2.

left femur, in the center of which was an area of rarefaction measuring 1 cm. in diameter.

An operation was performed on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JAMES J. MCCORT*: Was a differential count done on the smear of the blood?

DR. BENJAMIN CASTLEMAN: None was given.

DR. MCCORT: This patient had chronic osteomyelitis of the upper third of the left femur for twenty years. There had been many flare-ups of this process, with the formation of draining sinuses. A saucerization had been performed eight years previously, but symptoms persisted, only to subside upon the administration of penicillin. Two months prior to admission pain occurred in the low back and right thigh. It is not possible to be sure whether or not this described episode of low-back pain, coccydynia and right-thigh pain represented a recrudescence of a chronic focus of infection in the upper third of the left femur. The distribution of the pain makes it seem unlikely, as does the fact that it disappeared completely with nonspecific therapy. However, the radiolucent area seen in the sclerotic zone about the lesser trochanter of the left femur could indicate a persistent focus of infection.

Closely following this episode, pain and swelling were noted in the right shoulder. On the basis of a clinical diagnosis of bursitis, an anesthetic injection was given. It is unfortunate that a roentgenogram of the shoulder was not obtained prior to the initiation of this procedure. The presence of axillary adenopathy was a definite indication for x-ray examination. Nonetheless, there was some relief of symptoms following bursa injection. However, progressive swelling and pain developed later in the right upper arm.

At this point I might look at the admission roentgenogram. The upper third of the shaft of the humerus exclusive of the humeral head shows extensive bone destruction (Fig. 1). This involves the medullary portion of the bone as well as the cortex. Periosteal thickening and elevation are seen only along the upper inner margin. A definite soft-tissue mass is not seen although the overlying soft tissues are swollen and the normal muscle planes are poorly made out. The humeral joint does not appear to be involved. No new-bone formation is seen, nor is the shaft of the bone expanded by the destructive process. The swollen axillary lymph nodes that were palpable prior to admission are probably present but obscured by the soft-tissue swelling.

From the history, the physical findings and the x-ray appearance, the process in the right humerus seems most likely to represent a pyogenic osteomyelitis. That this was not improved by twelve days of penicillin therapy raises several questions. Was a large amount of encapsulated pus present? Was the organism penicillin fast? Was the drug given in inadequate doses? The infection was probably present prior to the injection of the bursa, but this procedure conceivably could have interfered with the local defense mechanisms and resulted in more rapid spread. The normal temperature, pulse rate and respiratory rate, as well as the white-cell count at the upper limits of normal, may have represented partial suppression by the penicillin therapy. The only laboratory finding seemingly not so affected was the elevated sedimentation rate.

Osteomyelitis due to other infections, such as tuberculosis, syphilis, typhoid, brucella and actinomycosis, must be considered, but there is no evidence to substantiate such a diagnosis. Tuberculosis usually begins in and around the joint. In syphilis the predominant picture is a periostitis with irregular cortical thickening. With typhoid or brucella osteomyelitis, systemic symptoms are

*Associate radiologist, Massachusetts General Hospital.

more pronounced. These types are rare in my experience. Osteomyelitis due to actinomycosis or other pathogenic fungi is also rare and results in multiple, draining sinuses to the skin.

Could this infectious process have been engrafted on a primary or metastatic malignant neoplasm of bone? In this patient's age group, reticulum-cell sarcoma, Hodgkin's disease and lymphosarcoma of the bone are seen. However, the bone lesion is usually part of a generalized process, no evidence of which exists in this patient. An occult primary carcinoma of the thyroid, breast, gastrointestinal tract, kidney or pelvic organs could give rise to a solitary bone metastasis in the humerus. Although this possibility is not excluded short of a biopsy, there is nothing from the clinical or x-ray standpoint in favor of it.

My impression, therefore, is that this patient had an acute osteomyelitis of the right humerus and a chronic sclerosing osteomyelitis of the left femur. The operation indicated probably was incision and drainage of the right humerus, with biopsy.

A PHYSICIAN: Does amyloid disease ever infiltrate the shaft of the bone and produce pain or a fracture?

DR. CASTLEMAN: Amyloid infiltration of the bone is extremely rare, and in the cases that have been reported, amyloid is usually present in other parts of the body before it goes to the bone.

Dr. Funsch, would you tell us the opinion on the Ward?

DR. ROBERT E. FUNSCH: When we saw this patient on the Service we believed that she had an infectious process. On the basis of the history, we did not think we could completely eliminate the possibility of neoplasm. We have seen many people with a definite focus of infection that is quiescent, but who show clinically active osteomyelitis elsewhere. She had had an operation some time before and had a recurrence of activity that was treated by penicillin. There was no reason to believe that that would eliminate the focus and sterilize the lesion; therefore we thought that she probably had an infection. The x-ray films and also the normal temperature, pulse and white-cell count made us consider tumor. A normal temperature and white-cell count are not unusual in osteomyelitis that has been treated with penicillin. Probably, the daily injection of penicillin given by the local physician was Crysticillin. That would be enough to knock down the temperature ordinarily seen.

CLINICAL DIAGNOSIS

Acute and chronic osteomyelitis.

DR. MCCORT'S DIAGNOSIS

Acute and chronic osteomyelitis.

ANATOMICAL DIAGNOSIS

Acute and chronic osteomyelitis of right humerus.

PATHOLOGICAL DISCUSSION

DR. FUNSCH: On the fourth day we explored this area through an incision at the midshaft of the humerus and went through a great deal of indurated soft tissue to the periosteum, which was not too well separated from the soft tissue bordering it. On incising the periosteum, we found creamy granulation tissue, not frank pus, that elevated the periosteum from the rather sclerotic shaft. We exposed an area of bone about 8 cm. long and found that the periosteum was elevated in this entire area. This, we thought, was evidence of subacute infection that had recently been well controlled. Then on resecting a piece of bone about 5 cm. long and about a third the circumference of the shaft, we encountered a cavity filled with granulation tissue and also 1 to 2 cc. of purulent material. We explored the cavity, curetted out débris and granulation tissue and finally reached what appeared to be normal cancellous bone. We placed a catheter in the wound and closed it. The patient was placed on penicillin for a twenty-one-day course.

DR. CASTLEMAN: Sections of the bone removed showed acute and chronic osteomyelitis. There was a large amount of purulent material in the soft tissue. Microscopically, in the bone there was a large amount of resorption of the vascular type. Many distended veins were seen filled with blood, which is what is usually seen in the acute form of osteomyelitis. The culture produced no growth. Apparently, the penicillin had killed most of the organisms or at least prevented them from growing on the usual culture mediums. We do not see osteomyelitis of this type very often nowadays. Fifteen years ago a chronic focus of bone infection with numerous areas appearing from one to many years after the primary osteomyelitis was not too uncommon. I suppose it is still seen occasionally by the Orthopedic Service.

The patient apparently has done very well.

DR. GORDON A. DONALDSON: Was there any indication for doing anything more to the femur?

DR. FUNSCH: No; I do not believe that there was. She had had penicillin, which is certainly effective in some of the cases. The orthopedic opinion is that, in an osteomyelitic lesion that may flare up occasionally but is well controlled by penicillin, surgical intervention is not indicated — except with a demonstrable sequestrum, which this patient did not have.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

"WHOSE MEDICINE?"

THE *Boston Herald*, in an editorial published on October 6, 1950, under the title "Whose Medicine?" expresses its disapproval of the major current activities and policies of the much maligned American Medical Association. The Association, in its bitter rear-guard action against the threat of "socialized medicine," according to the *Herald*, has backed itself into a dead end; it has failed to provide any real substitute for the Government's program, and its relations with the public have deteriorated as a result of its "crabbed negativism."

It may be that much of the criticism directed against the American Medical Association is deserved. If so, it must be taken as a blessing in whatever guise, and much of it is undoubtedly actuated by the most sympathetic of motives. The Association, after all, composed as it is of the rank and file of the country's practitioners is, like any other democratic institution, subject to the weaknesses and the errors that are inherent in mankind. When its faults are pointed out it must try and accept the correction and find comfort in the help that is so generously offered.

In this connection and seeking how best to bear the milde yoak that the *Herald* and other critics have fitted to him, the average physician, representative of the membership of the American Medical Association, cannot help noticing the *Herald's* apparent answer to its own question, "Whose Medicine?" as it appears on page fifty-six of the *Boston Sunday Herald* of October 29, 1950.

Here, reminiscent of the anti-histaminic banners so proudly hailed by so many newspapers a few months ago, appears the full-page announcement of an "amazing new discovery for rheumatism, arthritis — no faster arthritic pain relief known. . . safe — clinic tested — stops swelling of painful joints. . . contains sensational new research discovery," and so forth. Thus are portrayed the virtues of Imdrin, a secret patent remedy offered with a money-back "warranty," testimonial letters (one out of four of which states "I am not getting paid for these words") and the boast of clinic-testing by medical men with no names of clinics or physicians mentioned! Is this the *Herald's* medicine?

Although it is an obvious duty to resist the temptation of making comparisons between editorial rectitude on the one hand and business expediency on the other, to accuse the *Herald* of inconsistency would be impolitic and even embarrassing. Certain types of tobacco advertisements currently accepted by many medical journals put them also within the range of justifiable criticism although this error, it is said, will soon be corrected.

The friendship of the press, of which the *Herald* is such an outstanding representative, is far too valuable to be jeopardized in such a fashion. Its usual sympathetic understanding of the problems that attend the distribution of medical care, its honest reporting and its constructive criticism are all needed in these times.

Organized medicine, it may be hoped, is sufficiently broadminded and altruistic to profit by such

understanding and by any constructive criticism. It can only hope that its sincere critics give credit for the progress that is being made and appreciate the difficulties under which medical services are organized and delivered and, less frequently, paid for.

A UNITED STATES MEDICAL ACADEMY

LAST July two bills, H.R.9156 and H.R.9157, were introduced into the United States House of Representatives, each of which proposed the establishment of a United States medical academy analogous to the military establishments at West Point and at Annapolis. The philosophy behind them was that the students who attended would receive a medical education, in return for which they would be required to serve after graduation for five or six years in the armed forces.

The reasoning behind this philosophy seems plausible enough, but some of the details that have been written into these bills betray great lack of familiarity on the part of their authors with the machinery of modern medical education.

For example, an institution is proposed that would be four or five times as large as the present largest medical school. The concept of student selection envisaged by these proposals would be unique in the history of medical education, for it would be made according to the wishes of such office holders as the President, the Senators and the Representatives of the United States Government; another proposal is that students be apportioned according to geographic areas.

It was also suggested that the graduates of this medical academy be required to serve their internships in hospitals of the armed forces.

Of course, many of these difficulties could be adjusted and made suitable to the needs of present-day medical education. The changes that such adjustments would necessitate, however, would so alter the institution that it would probably not be recognized by its own sponsors.

The *Journal* is completely sympathetic with the aims of the gentlemen who proposed such measures as these; it agrees that more doctors are needed to support the rising standard of living in this nation, and it agrees that all able-bodied doctors owe to the military services of their country a certain fair proportion of their time and skill. The *Journal* fears, however, that such expansion as is here proposed would jeopardize the quality of medical education in the country and that any United States medical academy would have to be vigilantly protected against the natural and perhaps inevitable consequences of political impediments. There is in medical education as in other fields keen competition, and a United States academy would surely have to enter the lists and, to have a favorable chance in the national competition, would need to be most carefully planned from the ground up.

THE PEER P. JOHNSON LECTURE IN SURGERY

A NOTABLE occasion was marked at the Beverly Hospital on May 12, 1950, when Dr. Charles G. Mixter delivered the first annual Peer P. Johnson Lecture in Surgery, published elsewhere in this issue of the *Journal*.

In his introductory remarks Dr. Richard E. Alt explained that the lectureship had been established as a tribute to Dr. Johnson, long surgeon-in-chief of the Beverly Hospital, "in recognition of his many contributions to surgery," and that "a recognized leader in the science and art of surgery" would be chosen to present the address annually on Hospital Day. The lecture may be considered as honoring both the distinguished surgeon-in-chief of the Beverly Hospital and the eminent surgeon-in-chief, emeritus, of the Beth Israel Hospital. The *Journal* acknowledges the privilege of presenting this address in its pages.

FUNCTION OF THE BRAIN STEM

"OUR birth," according to the poet, writing somewhat cryptically after the manner of poets, "is but a sleep and a forgetting." Ordinary realists, inclined to associate birth with an awakening, may be mystified by this interpretation of the birth process but they do not know about the brain stem, nor did Wordsworth. Perhaps the segmental apparatus of the brain at the hour of birth becomes inactivated to bring post-partum sleep to what had

been a restless fetus; forgetting implies some antecedent knowledge.

In the brain stem, already charged with a number of functions, lies the mysterious mechanism that puts man to sleep and awakens him, a release from Northwestern University concludes. It is, in fact, the ultimate effect of lullabies, fatigue and Sanka; of pain and discomfort, of noise, anxiety, coffee and stemwinding alarm clocks on this portion of the anatomy that determines the unconsciousness or consciousness of the individual.

The brain stem, when suitably stimulated, is the sentinel that keeps awake the rest of the sensorium; when unstimulated it allows the whole organism to sleep: perchance to dream; when destroyed it leaves the animal whose wakefulness it controlled pathologically and permanently somnolent, lethargic or in coma.

No more, let it be hoped, may the brain stems of any who guard the citadels of democracy be allowed to nod under their weight of omniscience, or to atrophy and wither away. He that keepeth Israel may neither slumber nor sleep, and eternal vigilance is still "the condition upon which God hath given liberty to man."

"Beware of rashness," Lincoln once wrote to General Hooker, entirely without knowledge of the function of the brain stem, "but with energy and sleepless vigilance go forward and give us victories."

From the Shakers we receive our herbs, roots and extracts, in as pure a state as could be expected; yet the Shakers are not perfect (as is sometimes shown by their medicines) in the business.

Boston M. & S. J., *November 13, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

MERRITT — Silas V. Merritt, M.D., of Fall River, died on August 16. He was in his seventy-eighth year.

Dr. Merritt received his degree from Long Island College of Medicine in 1894. He was a former president of Bristol South District Medical Society and was a member of the staffs of Fall River General and Union hospitals. He was a fellow of the American Medical Association.

A brother, a half-sister, four nephews and four nieces survive.

CORRESPONDENCE

94TH INFANTRY DIVISION LECTURES

To the Editor: The medical units of the 94th (Bay State) Infantry Division are sponsoring for the third season a series of postgraduate lectures delivered by outstanding medical specialists and augmented by the finest medical films. Although the program is a diversified one and should appeal particularly to the general practitioner, the attendance response has been chiefly by physicians in special fields. We believe that the instructive and interesting nature of the lectures should be brought to the attention of general practitioners.

In this connection we should like to emphasize that members of the Academy of General Practice are given credit toward the fifty postgraduate hours required for the retention of active membership.

Dr. Francis D. Moore, Moseley Professor of Surgery at Harvard Medical School and surgeon-in-chief of the Peter Bent Brigham Hospital, will deliver the lecture scheduled for November 30 in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston. His subject will be "Shock" and should be of general interest not only because of Dr. Moore's outstanding research in this field but also because of the tremendous surgical significance of this subject in view of the tense international situation.

Our series in the past have received general approbation, and we should like to continue the excellent selection of subjects and speakers. We therefore look forward to a greater response from the general practitioners in the metropolitan area.

WILLIAM H. CHASEN, M.D.
Lt. Col. M.C. (USAR)
Division Surgeon, 94th Infantry Division
147 Samoset Avenue
Quincy, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Bibliography in Audition. Vol. I, A-M. Vol. II, N-Z. 4°, paper (Vol. I, 220 pp.; Vol. II, 195 pp.). Cambridge: Harvard University, Psycho-Acoustic Laboratory, 1950.

This monumental reference work endeavors to cover completely the literature of the various aspects of audition for the period 1938–1948, and reasonably complete for the pre-1938 literature. The work is recommended for all medical and public libraries.

The Common Infectious Diseases: A handbook for students and postgraduates. By H. Stanley Banks, M.A., M.D. (Glas.), F.R.C.P. (Lond.), D.P.H. (Cantab.), physician-superintendent, Park Hospital, Hither Green, London, and lecturer in infectious diseases, the Medical College, St. Bartholomew's Hospital, University of London. 8°, cloth, 354 pp., with 90 illustrations and 8 tables. Baltimore: Williams and Wilkins Company, 1949. $4.50.

This manual is based on the teaching of the author at St. Bartholomew's Hospital in London. The material on each disease has been brought up to date. Included with the ordinary infectious diseases, as known in this country, are glandular fever, poliomyelitis, acute diarrhea and infective gastroenteritis in infants. Lists of selected references are appended to the various chapters, and there is a good index. The publishing is excellent. The printing was done in Great Britain.

Danger! Curves Ahead! How to Prevent and Correct Overweight. By Miriam Lincoln, M.D., clinical assistant professor of medicine, School of Medicine, University of Washington. 8°, cloth, 138 pp., with illustrations by Florenz Clark. New York: Macmillan Company, 1948. $2.50.

This small volume on obesity, written for the laity by a competent physician, is well done. The various aspects of overweight are discussed in simple, understandable language. The major portion of the text is devoted to dietary measures. A valuable table of foods and their caloric contents concludes the text. The publishing is good, and the book should be in all collections of popular medicine.

NOTICES

ANNOUNCEMENTS

Dr. Bartlett H. Stone announces the opening of an office for the practice of obstetrics and gynecology at 1101 Beacon Street, Brookline.

Dr. Peter F. Weiss announces the removal of his office to 36 Perkins Street, Jamaica Plain, Boston.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the Boston City Hospital House Officers' Association will be held in the Dowling Amphitheater of the Hospital on Tuesday, November 21, at 5 p.m. Dr. Frank H. Lahey, chief of the Lahey Clinic, will speak on the subject "Diseases of the Ileum, Colon and Rectum."

Interested persons are invited to attend. (This lecture is at 5 p.m. rather than 7 p.m., the hour for all the other lectures in this series.)

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts General Hospital at New England Mutual Hall, 225 Clarendon Street, Boston, on Monday, November 27, at 8 p.m., Dr. Edward F. Bland presiding.

PROGRAM

The Surgical Relief of Portal Hypertension. Drs. Robert R. Linton and Chester M. Jones.

Summary of a Research on Coronary-Artery Disease in Youth. Drs. Paul D. White and Menard Gertler and Stanley Garn, Ph.D.

Rheumatic Fever and Rheumatic Heart Disease: A twenty-year report on 1000 patients followed since childhood. Drs. Edward F. Bland and T. Duckett Jones.

Aortitis and Aortic Valvulitis Associated with Rheumatoid Arthritis. Drs. William S. Clark, J. Peter Kulka and Walter Bauer.

Physiologic and Physical Laws that Govern the Clinical Appreciation of Cardiac Thrills. Drs. Timothy B. Counihan, Howard B. Sprague and Maurice B. Rappaport.

Cardiac Catheterization Studies of the Action of Protoveratrine on the Circulation of Hypertensive Patients. Drs. Gordon S. Myers, J. Gordon Scannell, Allen B. Barbour, Ernest Craige, Thomas W. Mattingly and James H. Currens.

Interested physicians and medical students are cordially invited to attend.

BETH ISRAEL HOSPITAL HOUSE OFFICERS' COLLOQUIA

The first three lectures of the Beth Israel Hospital House Officers' Colloquia will be presented in the auditorium of the Hospital at 8 p.m. On November 20 Dr. Mark D. Altschule will speak on the subject "Recent Advances in a Backward Field." On November 27 Dr. William Dameshek will speak on the subject "Hypersplenism." On December 4 Dr. Sidney Farber will speak on the subject "The Chemotherapy of Neoplasms."

94TH INFANTRY DIVISION LECTURE

The lectures sponsored by the 94th (Bay State) Infantry Division will be continued on Thursday, November 30, at 8 p.m., in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston.

Dr. Francis D. Moore, Moseley Professor of Surgery at Harvard Medical School and surgeon-in-chief at the Peter Bent Brigham Hospital, will speak on the subject "Shock."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 1–29. Springfield Hospital. Page 679, issue of October 26.

NOVEMBER 17. Society of American Bacteriologists, Northeast Branch. Page 722, issue of November 2.

NOVEMBER 20. Hartford Medical Society. Page 680, issue of October 26.

NOVEMBER 20. Beth Israel Hospital House Officers' Colloquia. Notice above.

NOVEMBER 21. South End Medical Club. Page 721, issue of November 2.

NOVEMBER 21. Boston City Hospital House Officers' Association. Notice above.

NOVEMBER 27–JUNE 4. New England Cardiovascular Society. Page 680, issue of October 26.

NOVEMBER 27. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

NOVEMBER 27. New England Cardiovascular Society. Notice above.

NOVEMBER 27. Beth Israel Hospital House Officers' Colloquia. Notice above.

NOVEMBER 28. Norfolk District Medical Society. Page 629, issue of October 19.

NOVEMBER 30. 94th Infantry Division Lecture. Notice above.

DECEMBER 4. Beth Israel Hospital House Officers' Colloquia. Notice above.

DECEMBER 4. Hartford Medical Society. Page 680, issue of October 26.

DECEMBER 7–9. New York State Society of Anesthesiologists. Page 582, issue of October 12.

DECEMBER 9. American Federation for Clinical Research. Page 680, issue of October 26.

DECEMBER 14. Treatment of Hyperthyroidism, Especially with Radioactive Iodine. Dr. Earle Chapman. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

DECEMBER 18. Hartford Medical Society. Page 680, issue of October 26.

JANUARY 3. Hampshire District Medical Society. Page 170, issue of July 27.

JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.

APRIL 9–13. American College of Physicians. Page 296, issue of June 15.

APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 24–26. American Goiter Association. Columbus, Ohio.

NOVEMBER 10–21, 1951. Pan-Pacific Surgical Association. Page 680, issue of October 26.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

NOVEMBER 28.
JANUARY 23.
FEBRUARY 27.
MARCH 27.
APRIL 24.
MAY 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

(*Notices concluded on page xv*)

NOTICES (*Concluded from page 798*)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 23

FRIDAY, NOVEMBER 24

*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*12:00 m.–1:30 p.m. Surgical Pathological Conference. Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.
*2:00–4:00 p.m. Therapeutic Conference. Joseph H. Pratt Diagnostic Hospital.
*4:00–6:00 p.m. X-Ray Conference. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, NOVEMBER 25

*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 27

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting, Harris Hall, New England Deaconess Hospital.
*8:00 p.m. New England Cardiovascular Society. New England Mutual Hall, Boston.
8:00 p.m. Beth Israel Hospital House Officers' Colloquia. Beth Israel Hospital, Boston.

TUESDAY, NOVEMBER 28

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, NOVEMBER 29

*12:00 m. Outside speaker. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

POSTGRADUATE DIVISION
TUFTS COLLEGE MEDICAL SCHOOL

Courses for the General Practitioner

ELECTROCARDIOGRAPHY I, December 4-8, 1950

This course is designed to familiarize the physician with the interpretation of electrocardiograms. It covers the newer developments in this field, including unipolar extremity leads and complete 12-lead tracings. Lectures and demonstrations supplement supervised intensive study of electrocardiographic records. Minimum enrollment: 30. Tuition fee: $40. Dr. H. Magendantz in charge.

OPHTHALMOLOGY, January 8–February 2, 1951

The commoner external eye diseases and their treatment are taught through demonstration of patients. Instruction is given in the proper use of the ophthalmoscope, with interpretation of the normal fundus and fundus lesions in relation to general medicine. Enrollment limited to 5. Tuition fee: $75. Dr. J. Igersheimer in charge. (The course is given Monday, Wednesday and Friday mornings only.)

ELECTROCARDIOGRAPHY II, January 15-17, 1951

A continuation course for those who have taken Electrocardiography I or have had previous experience in the interpretation of electrocardiograms. Minimum enrollment: 15. Tuition fee: $25. Dr. H. Magendantz in charge.

RHEUMATIC DISEASES, February 5-7, 1951

The rheumatic diseases, the medical aspects of bone diseases, and the consequences of injury to bones and joints are reviewed with emphasis on differential diagnosis, complications, and therapy. Minimum enrollment: 10. Tuition fee: $30. Dr. H. Brugsch in charge.

The catalog of courses for the academic year 1950-51 and application cards will be sent on request.

POSTGRADUATE DIVISION

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Supplements the sun...
removes the shadow of ***RICKETS***

Rickets may be found in apparently healthy and well nourished infants due to an insufficient intake of vitamin D plus inadequate exposure to ultraviolet rays.

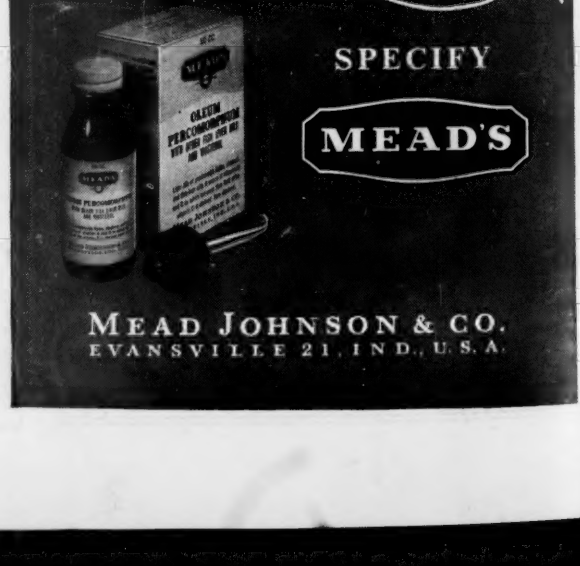
It is now generally accepted that a vitamin D supplement should be given regularly not only to infants but to older children and adolescents. Mead's Oleum Percomorphum With Other Fish Liver Oils and Viosterol is useful for this purpose.

Mead's Oleum Percomorphum

1. Is a highly potent† source of natural vitamins A and D.

2. May be given in drop doses that are easily administered and well tolerated, and is supplied in capsule form also.

3. Has a background of sixteen years of successful clinical use.

†Potency: 60,000 U.S.P. units of vitamin A and 8500 U.S.P. units of vitamin D per gram. Each drop supplies 1250 units of vitamin A and 180 units of vitamin D; each capsule, 5000 units of vitamin A and 700 units of vitamin D.

Supplied in 10 cc. and 50 cc. bottles; and in bottles of 50 and 250 capsules.